Medical Genetics

Basic Genetics

Basic Concepts of Molecular Genetics & Pathogenetics

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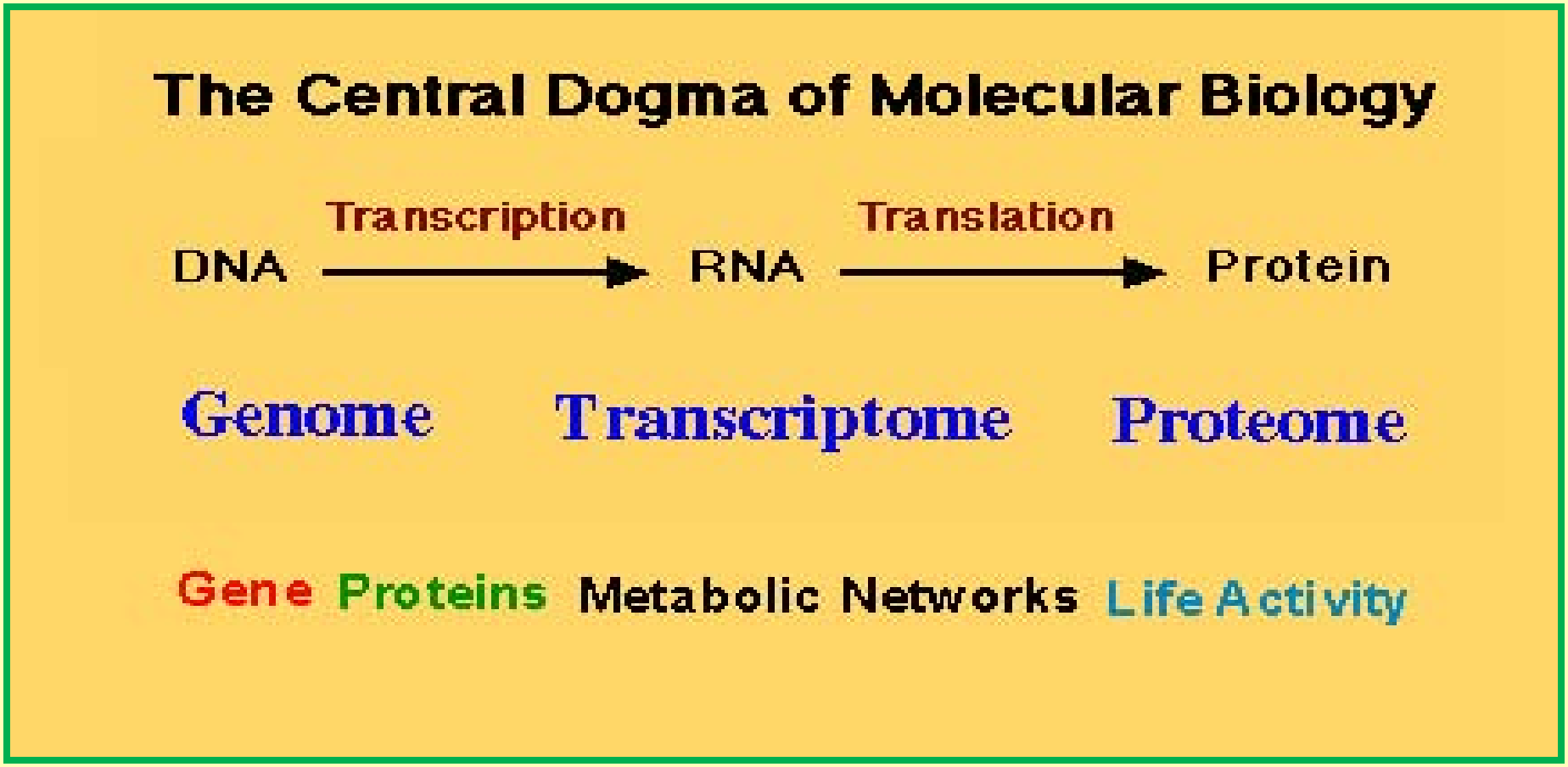
Spectrum of Medical Genetics

Basic Genetics	Clinical Genetics
Part I: Molecular Genetics Part II: Biochemical Genetics Part III: Physiological Genetics Part IIII: Cytogenetics Part V: Pathogenetics Part VI: Pharmacogenetics Part VII: Oncogenetics Part VIII: Immunogenetics Part IX: Formal Genetics Part X: Population genetics Part XI: Developmental Genetics Part XII: Genomics Part XIII: Transcriptomics Part XIV: Proteomics	Part I: Chromosomal Aberrations Part II: Congenital Malformations Part III: Inborn Errors of Metabolism Part IV: Mitochondrial Disorders Part V: Genetic Systemic Syndrome Part VI: Genetic Diseases of The Nervous system Part VII: Genetic Diseases of The Endocrinal system Part VIII: Genetic Diseases of The Cardio-Vascular system Part IX: Genetic Diseases of The Respiratory system Part X: Genetic Diseases of The Gastro-Intestinal system Part XI: Genetic Diseases of The Urinary system Part XII: Genetic Diseases of The Muscular system Part XIII: Genetic Diseases of The Skeletal system Part XIV: Genetic Diseases of The Blood system Part XV: Genetic Diseases of The Immunity system Part XVI: Genetic Diseases of The Male Genital system Part XVII: Genetic Diseases of The Female Genital system Part XVIII: Genetic Diseases of The Ocular system Part XIX: Genetic Diseases of The Auditory system Part XX: Genetic Diseases of The Skin Part XXI: Genetic Psychiatric Disorders
Diagnostic Genetics	**Therapeutic Genetics**
Part I: Molecular Diagnostic Techniques Part II: Cytogenetic Diagnostic Techniques Part III: Biochemical Diagnostic techniques Part IV: Prenatal Diagnosis Part V: Pre-Implantation Diagnosis Part VI: Per-Symptomatic Diagnosis Part VII: Conventional Diagnostic Techniques	Part I: Pharmacologic Therapy Part II: Nutritional Therapy Part III: Replacement Therapy Part IV: Transplantation Therapy Part V: Stem Cell Therapy Part VI: Surgical Intervention Part VII: Genetic Therapy Part VIII: Fetal Therapy Part IX: Conventional Therapy
Prophylactic Genetics	**Applied Genetics**
Part I: Pre-Conception Prophylaxis Part II: Pre-Natal Prophylaxis Part III: Pre-Symptomatic Prophylaxis	Part I: Forensic Genetics Part II: Genetic Counseling Part III: Genetic Screening Part IV: Genetic Engineering Part V: Eugenics

Relation Between Genes and Life

The genetic material controls the synthesis of proteins and enzymes which are the actual and direct mediators of all life processes living cells.



Dogma Of Molecular Pathology In Health And Disease

Genome → Transcriptome → Proteome

Transcriprion — Translation

DNA → mRNA → Protein

Gene — Protein — Metabolic Network — Cellular Function — Life Activity

Mutant Gene → Abnormal mRNA

↓

Deficient/Defective/Excess Product

Protein (Structural/Catalytic) – RNA

↓

Disturbed Metabolic Networks → Disturbed Cell Function

↓

Deranged Physiological Activities → Disease

↓

Genetic Disorder – Immunodeficiency – Congenital Anomaly – Cancer

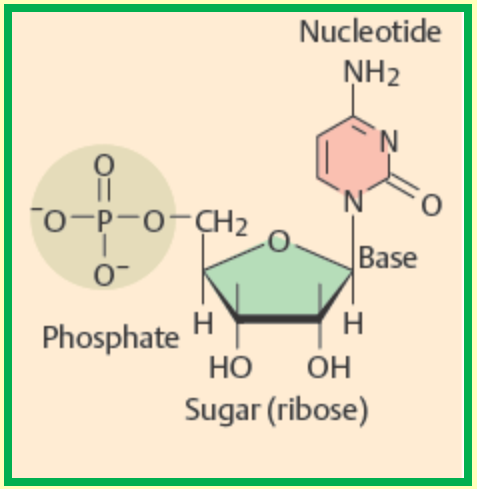
Structure Of The Genetic Material

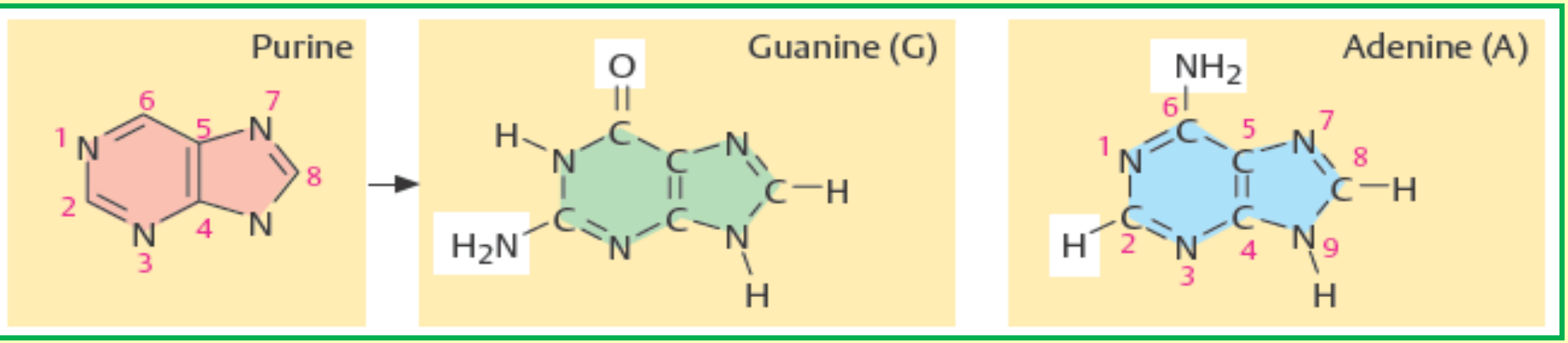
The building components of the genetic material in all living creatures are the nucleic acids. There are two main categories of nucleic acids: DNA or Deoxyribo-Nucleic Acid and RNA or Ribo-Nucleic Acid.

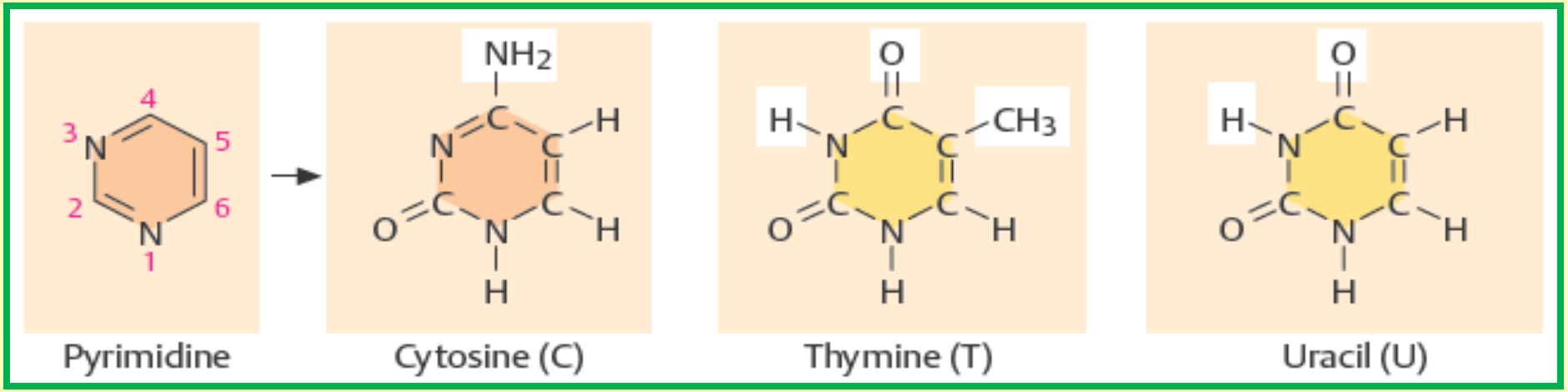
Nucleic acids are very long unbranched hetero-polymers, composed of large number of similar monomers : the nucleotides, which are the building blocks of the nucleic acids.

Each nucleotide is composed of an inorganic phosphate group attached to a 5-carbon atom sugar, ribose sugar in RNA and 2-deoxyribose sugar in DNA, to which is attached a nitrogenous base.

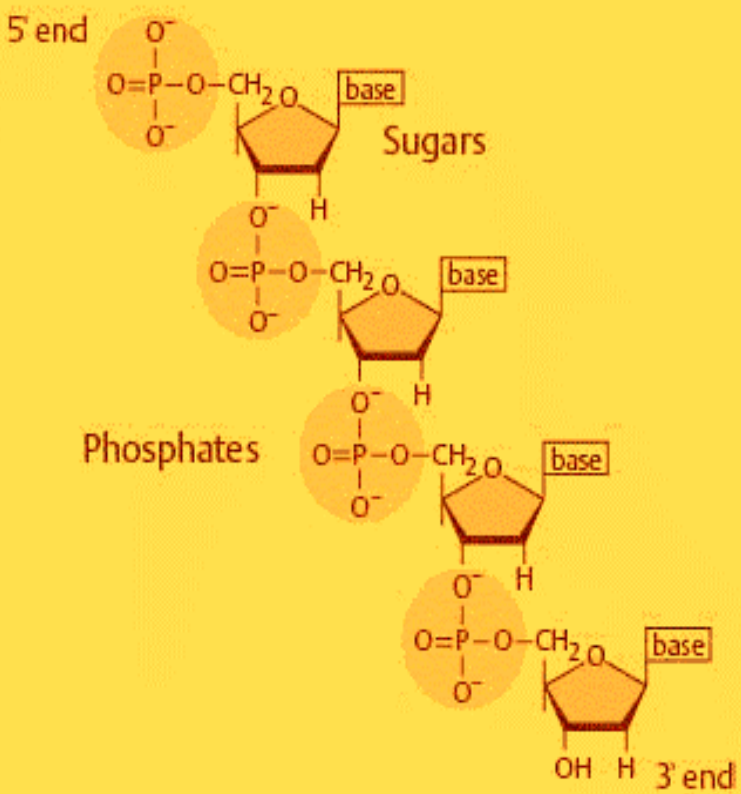
Five different bases participate in formation of five different nucleotides that build up the nucleic acids. The bases are either purine bases : adenine (A) and guanine (G), or pyrimidine bases : cytosine (C), thymine (T), and uracil (U). The nucleotides are usually referred to by the type of base they contain, hence we have (T), (C), (G), (A) and (U) nucleotides. The first four nucleotides are found exclusively in DNA, and Uracil replaces Thymine in RNA.


Nucleotide
Base
Phosphate
Sugar (ribose)

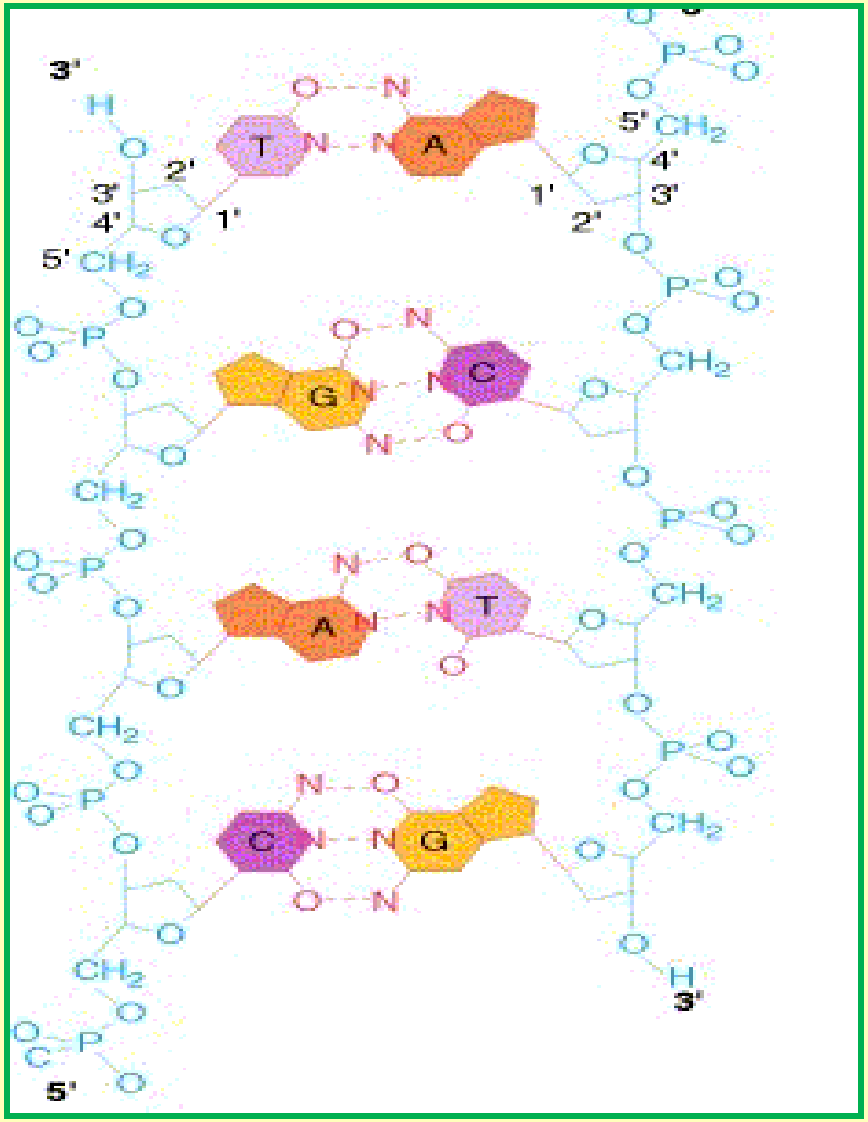

Purine
Guanine (G)
Adenine (A)


Pyrimidine
Cytosine (C)
Thymine (T)
Uracil (U)

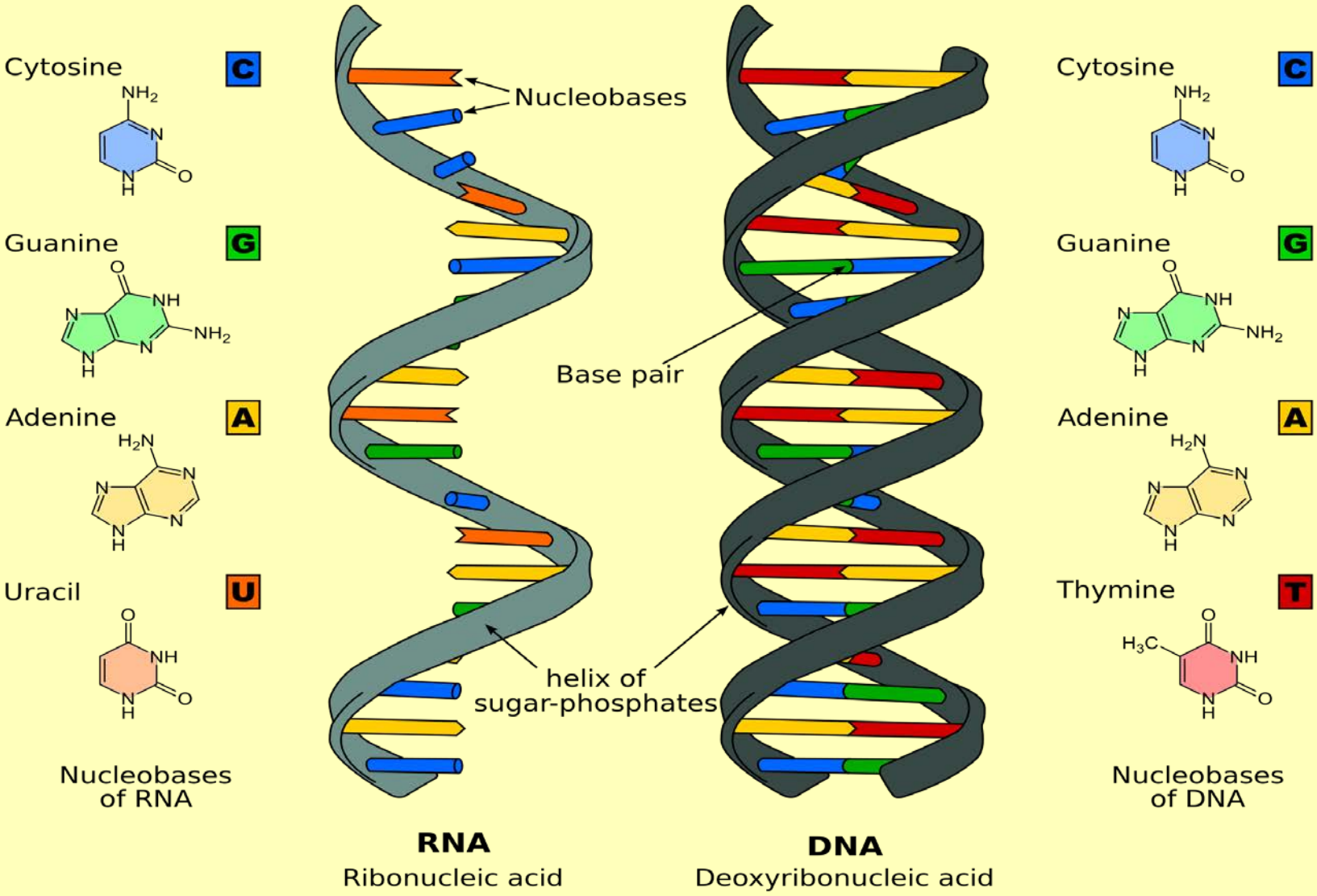
Structure Of The Genetic Material
The Nucleic Acids



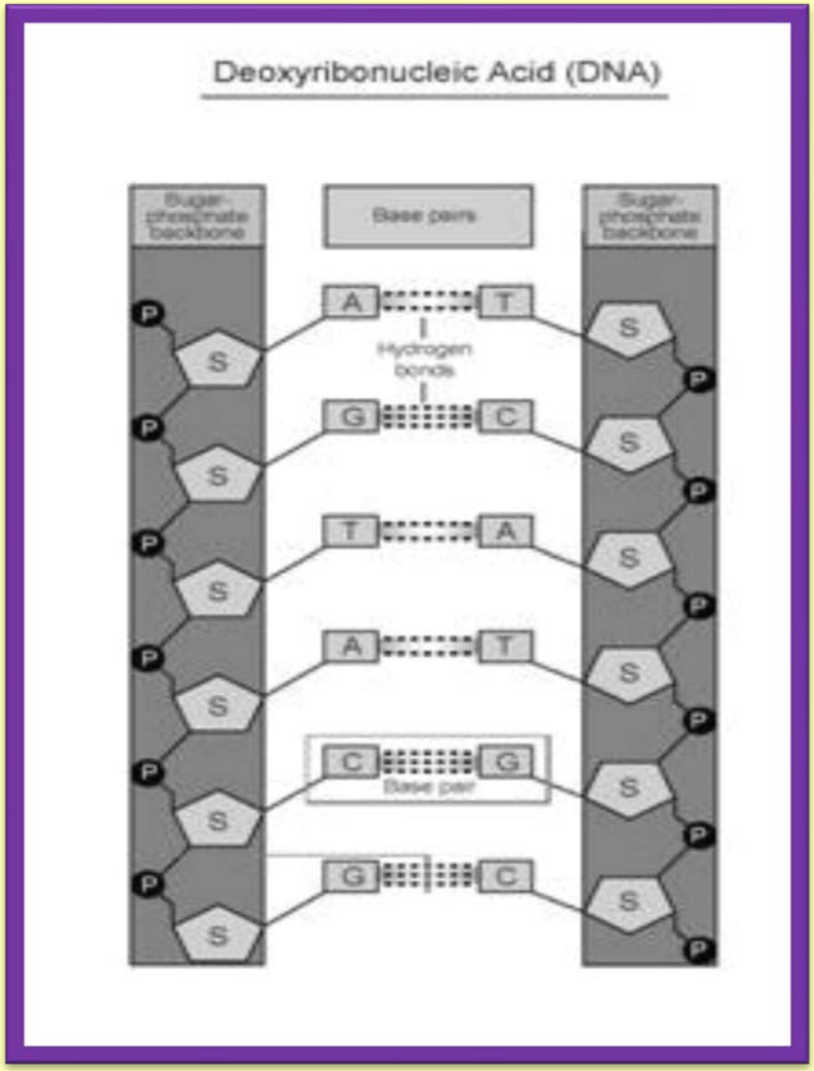
The longitudinal strand-shaped structure of the nucleic acids

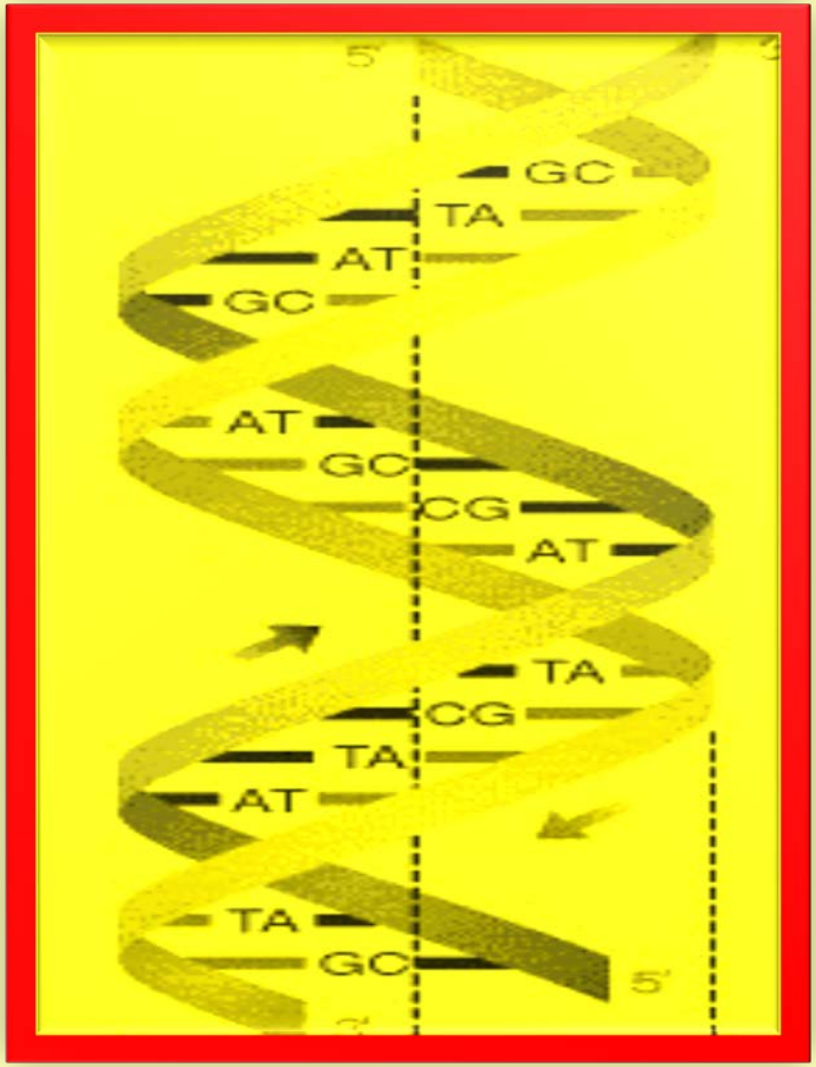


Structure of Nucleic Acids



DNA Structure & The Concept Of Base Complementarity





The longitudinal strand-shaped structure of the nucleic acids is maintained by the side-by-side attachment of the nucleotides, with the phosphate group of one nucleotide being attached to the ribose sugar of the next nucleotide.

DNA occurs naturally as a double stranded structure composed of two complementary strands attached together by the hydrogen bonds of the nitrogenous bases of each two opposing nucleotides. With few exceptions, RNA exists as a single stranded structure.

TYPES AND FUNCTIONS OF RNA

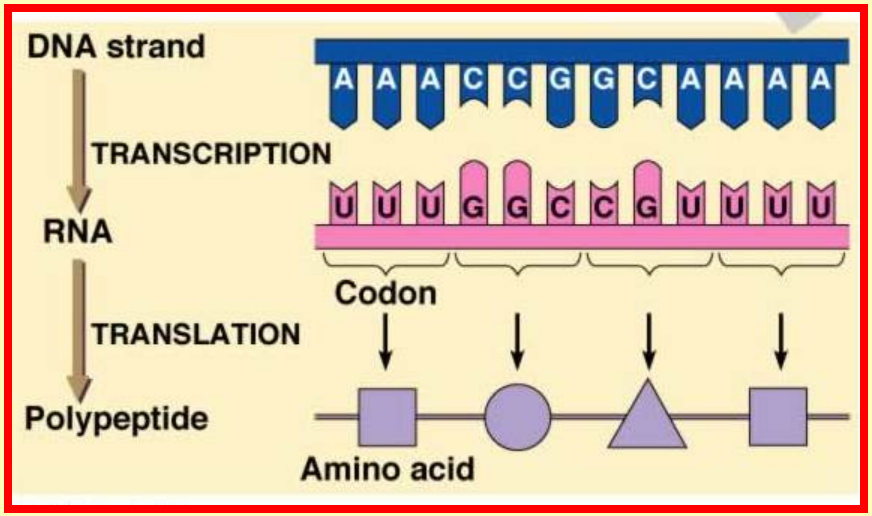
Currently, four main types of RNA have been well characterized both structurally and functionally. These are :

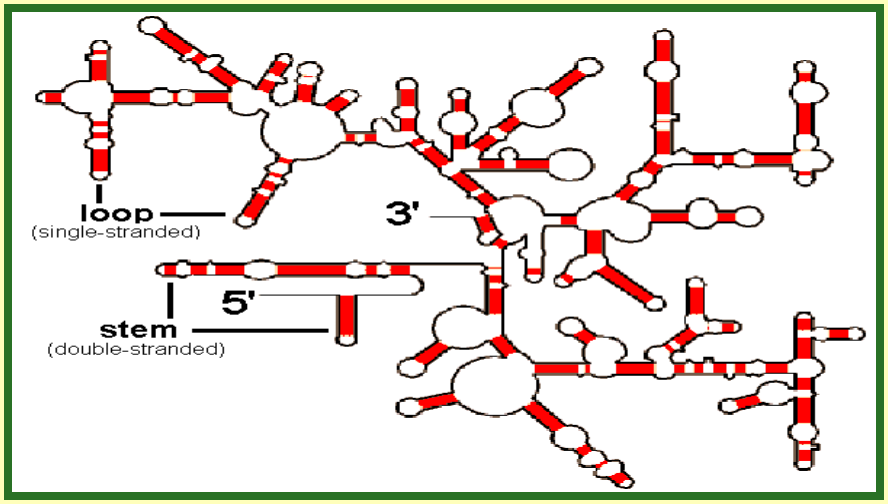
1. Messenger RNA (mRNA) : which is the main product and mediator of transcription, carrying the information necessary for protein synthesis.

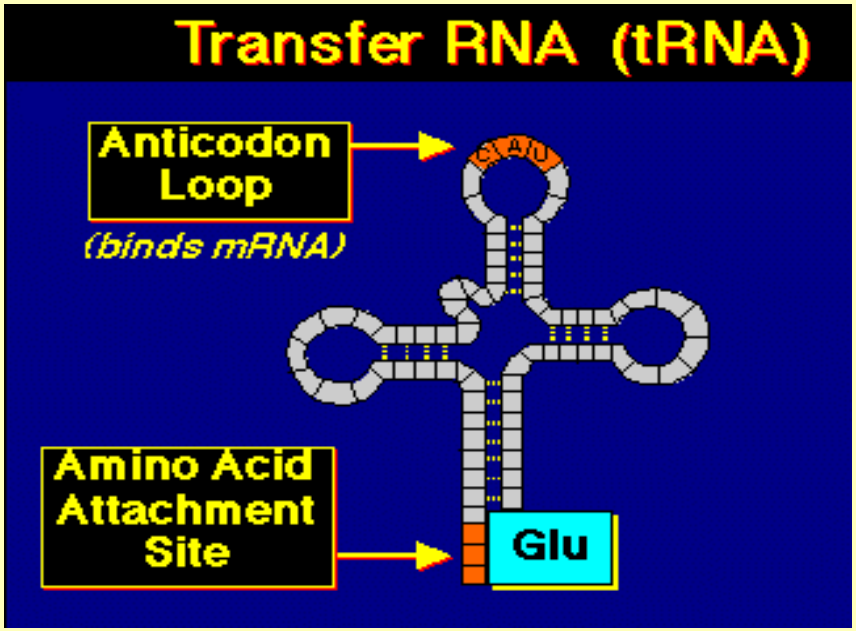
2. Ribosomal RNA (rRNA) : which functions in translation via decoding the mRNA code to recognize the amino acid defined by the specific codon.

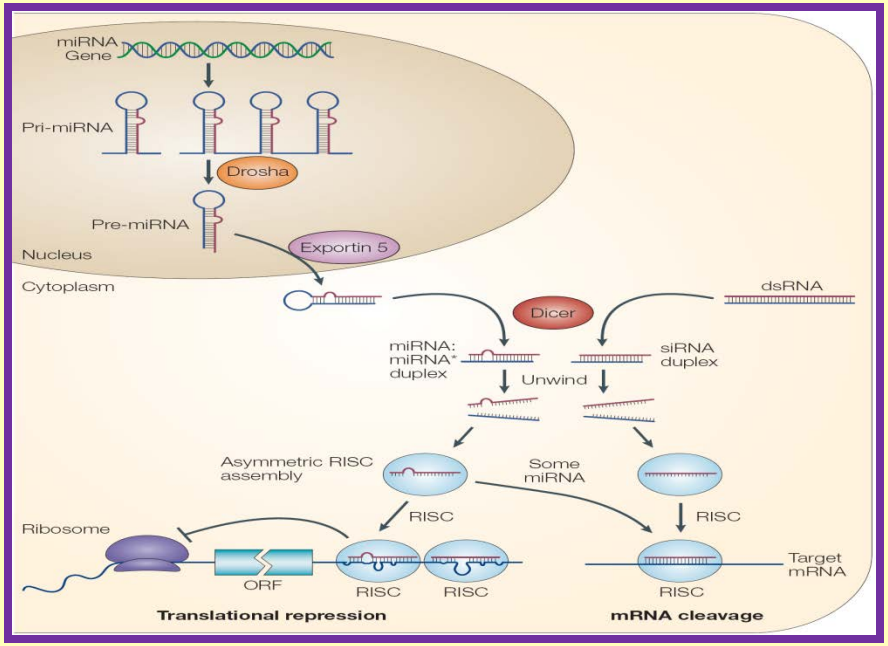
3. Transfer RNA (tRNA) : which also functions in translation via decoding the mRNA code to recognize the amino acid defined by the specific codon in addition to getting the amino acid from the cytosol to site of protein synthesis.

Functional Categories Of RNAs







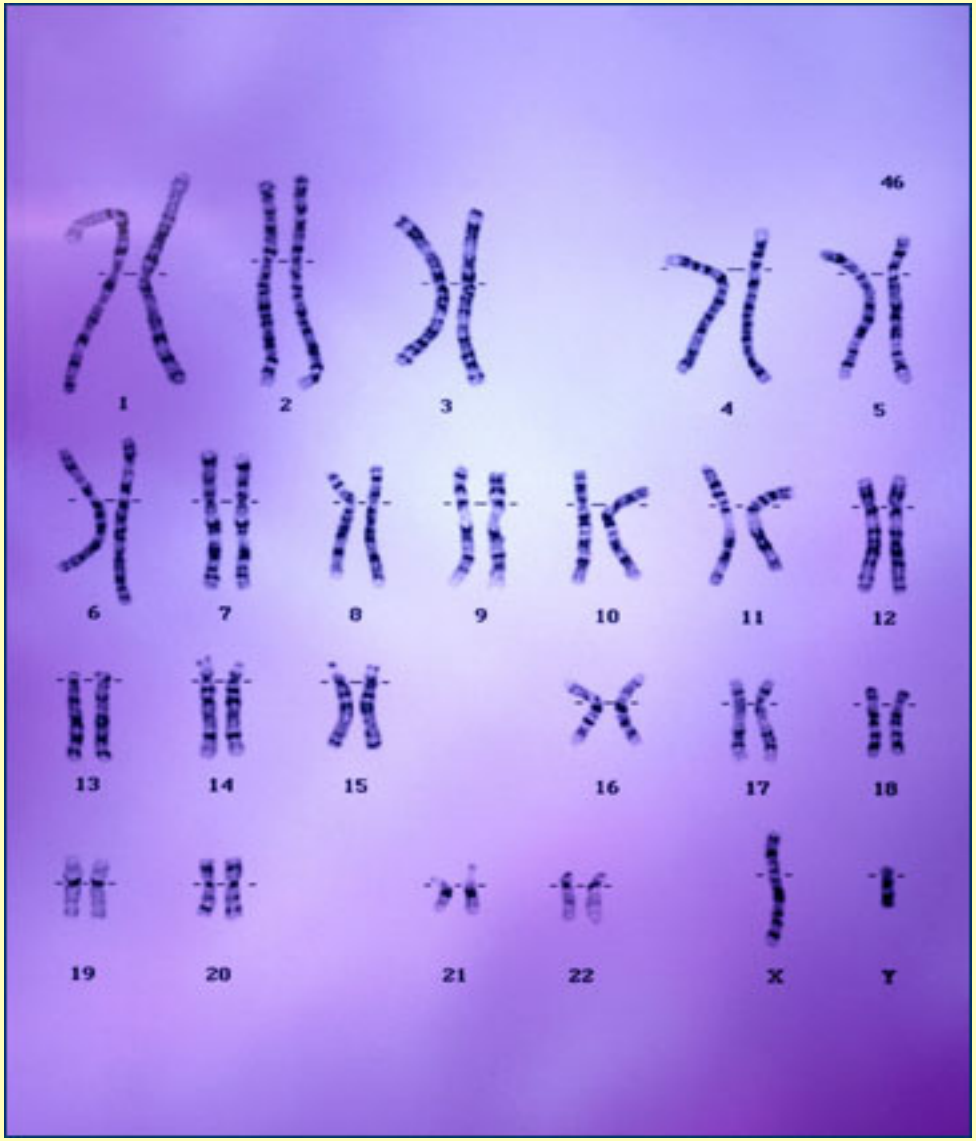


Organization OF The Genetic Material

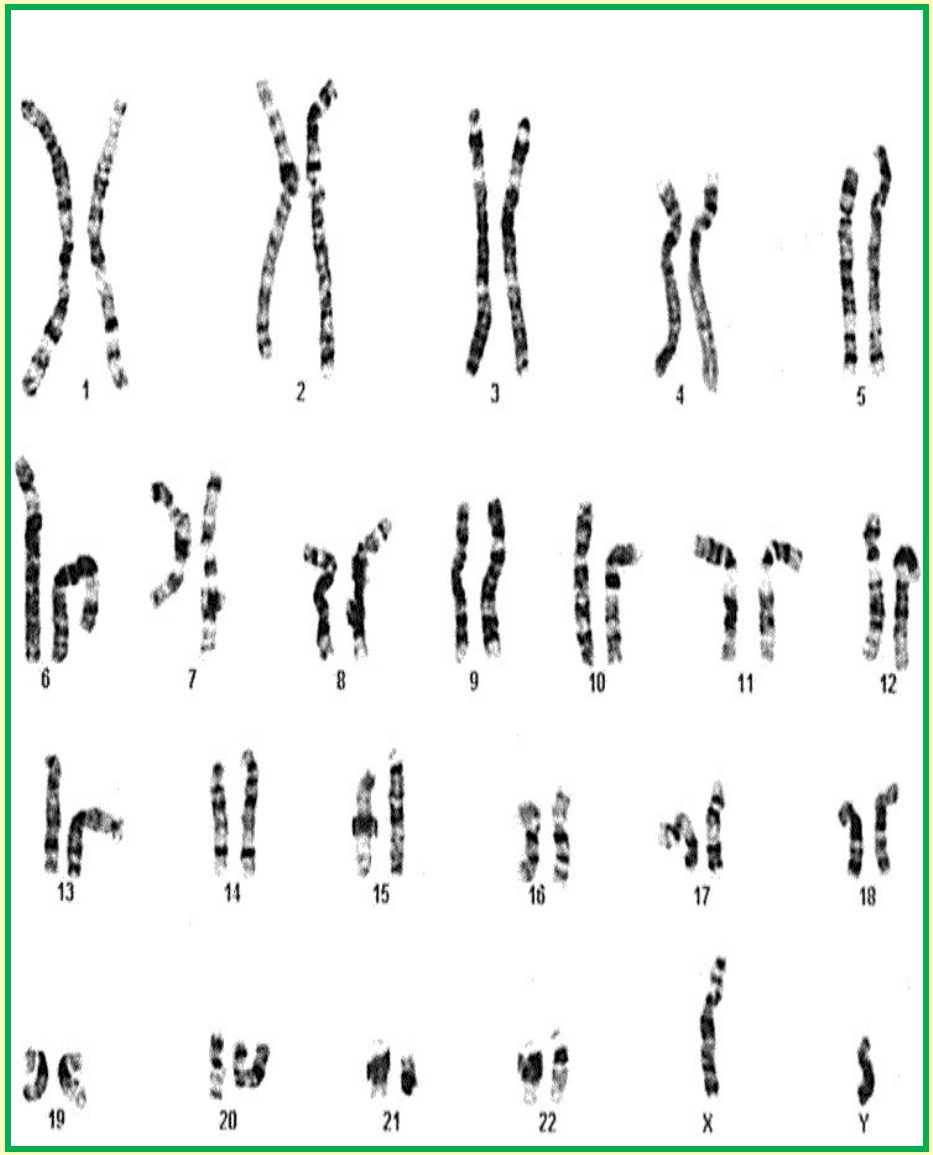
In human cells, the genome is unequally distributed into a major part, constituting more than 99.999 % of its size, organized in the form of long strands, open-ended chromosomes contained in the nucleus and referred to as the nuclear genome which comprises between 25000–38000 genes distributed over the chromosomes.

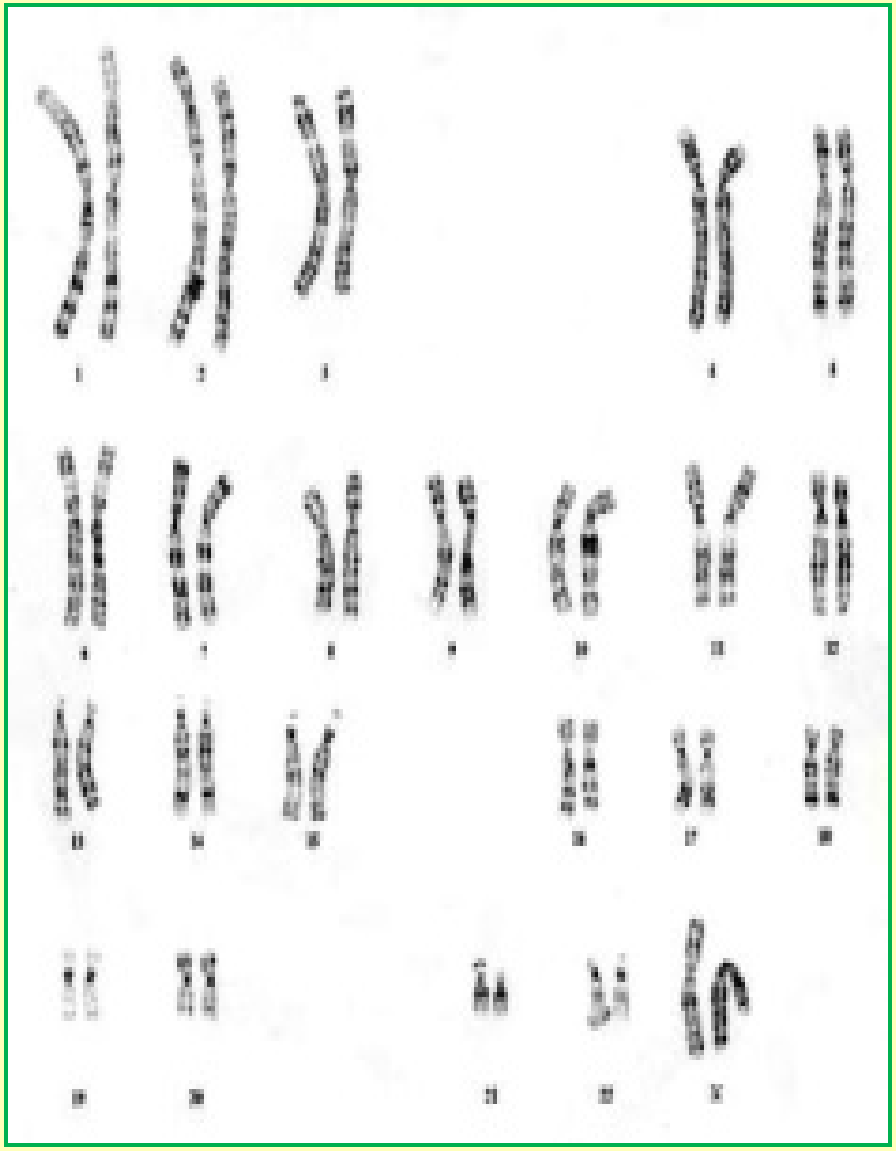
The remaining tiny part of the human genome exists in the form of varying numbers, tens to thousands, of very small closed circular double stranded structures present inside the mitochondria and is referred to as the mitochondrial genome. Each molecule of the mitochondrial genome (mtDNA) consists exclusively of 37 genes

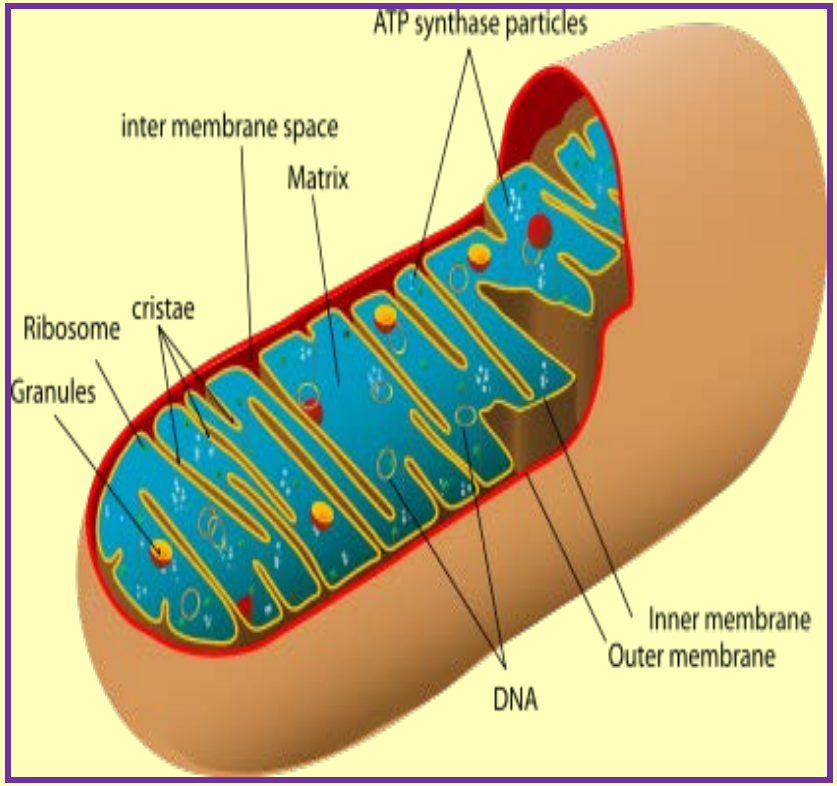
Organization Of The Nuclear Genome As Chromosomes

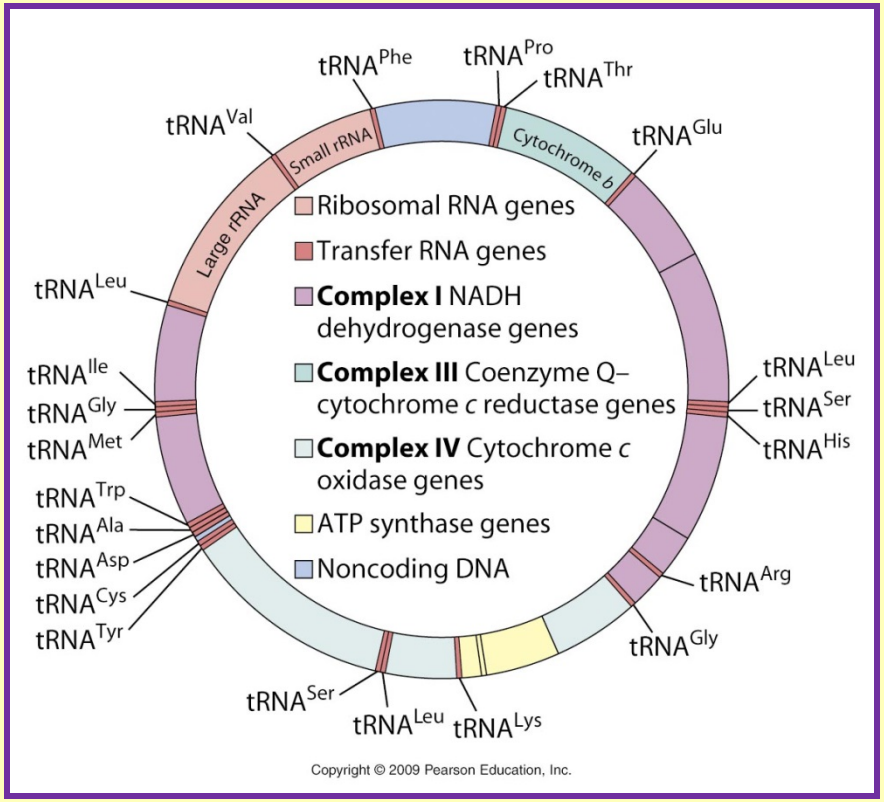


Normal Male (46,XY) And Female Karyotypes (46,XX)






ATP synthase particles
inter membrane space
Matrix
Ribosome
cristae
Granules
Inner membrane
Outer membrane
DNA


tRNA Phe
tRNA Pro
tRNA Thr
tRNA Val
tRNA Glu
Small rRNA
Cytochrome b
Large rRNA
Ribosomal RNA genes
Transfer RNA genes
Complex I NADH dehydrogenase genes
Complex III Coenzyme Q–cytochrome c reductase genes
Complex IV Cytochrome c oxidase genes
ATP synthase genes
Noncoding DNA
tRNA Leu
tRNA Ile
tRNA Gly
tRNA Met
tRNA Leu
tRNA Ser
tRNA His
tRNA Trp
tRNA Ala
tRNA Asp
tRNA Cys
tRNA Tyr
tRNA Arg
tRNA Gly
tRNA Ser
tRNA Leu
tRNA Lys
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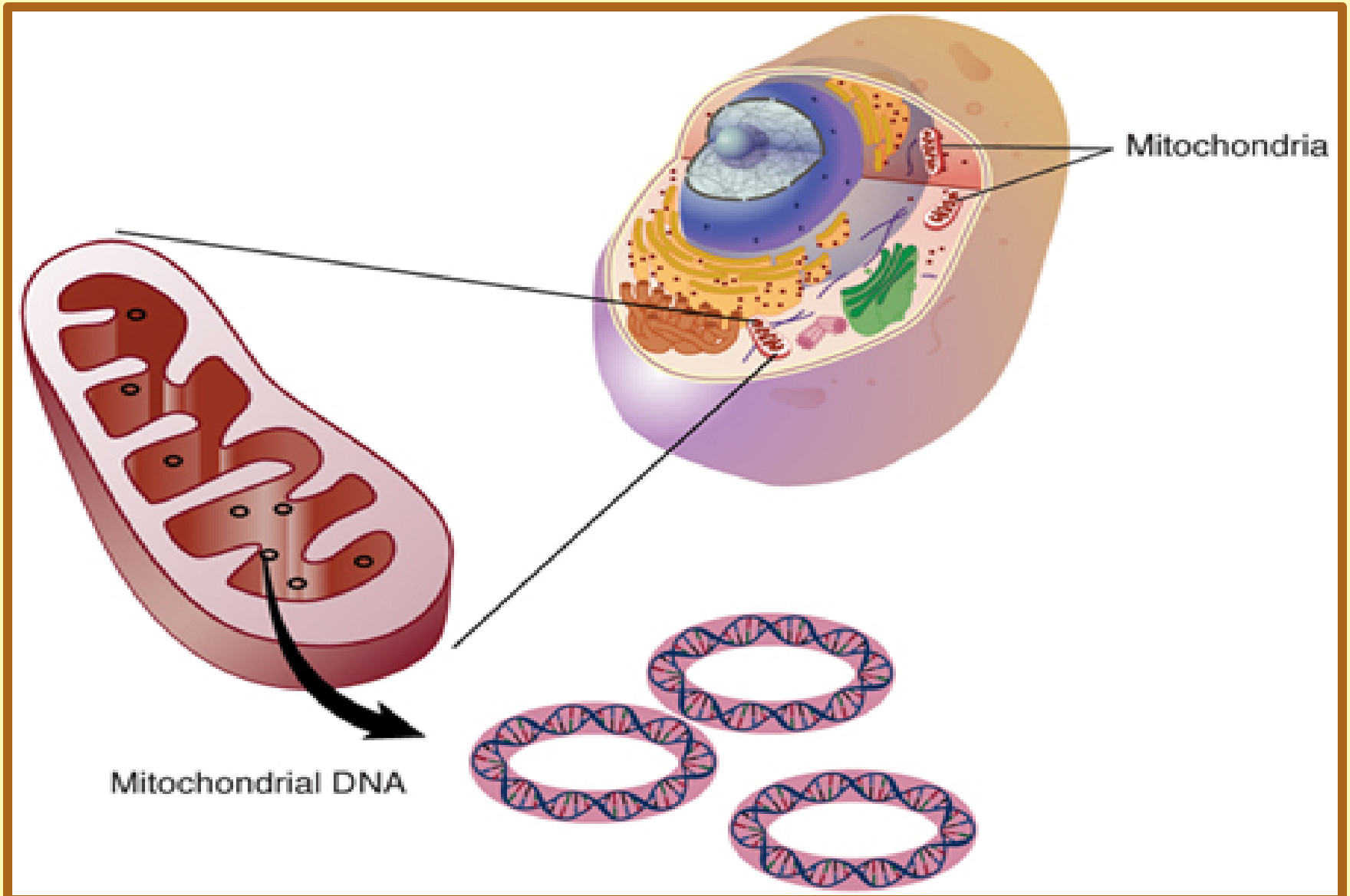
Mitochondrial DNA



Though it constitutes a very tiny fraction of the whole genome, mtDNA is indispensable for life because it codes for proteins that mediate ATP production in the cell in addition to many other important functions like apoptosis and many other vital metabolic activities like lipid oxidation and steroid biosynthesis.

The number of mitochondria and the number of mtDNA molecules in each mitochondrion varies according to the metabolic activities of the cell. The most active and energy-demanding cells, like neurons, heart muscles, the retina, skeletal muscles, endocrine glands, kidney cells and liver cells have the largest numbers of mitochondria within their cytoplasm and the largest numbers of mtDNA molecules in each mitochondrion as well.

The nuclear genome in each human germ cell, ovum and sperm, is organized into a set of 23 separate chromosomes known as the haploid genome which represents the unit genome of humans.

Upon fertilization, both haploid genomes of the sperm and the ovum constitute a diploid genome consisting of their 46 chromosomes that characterizes the nuclear genome of the zygote as well as of all somatic cells descendant from it.

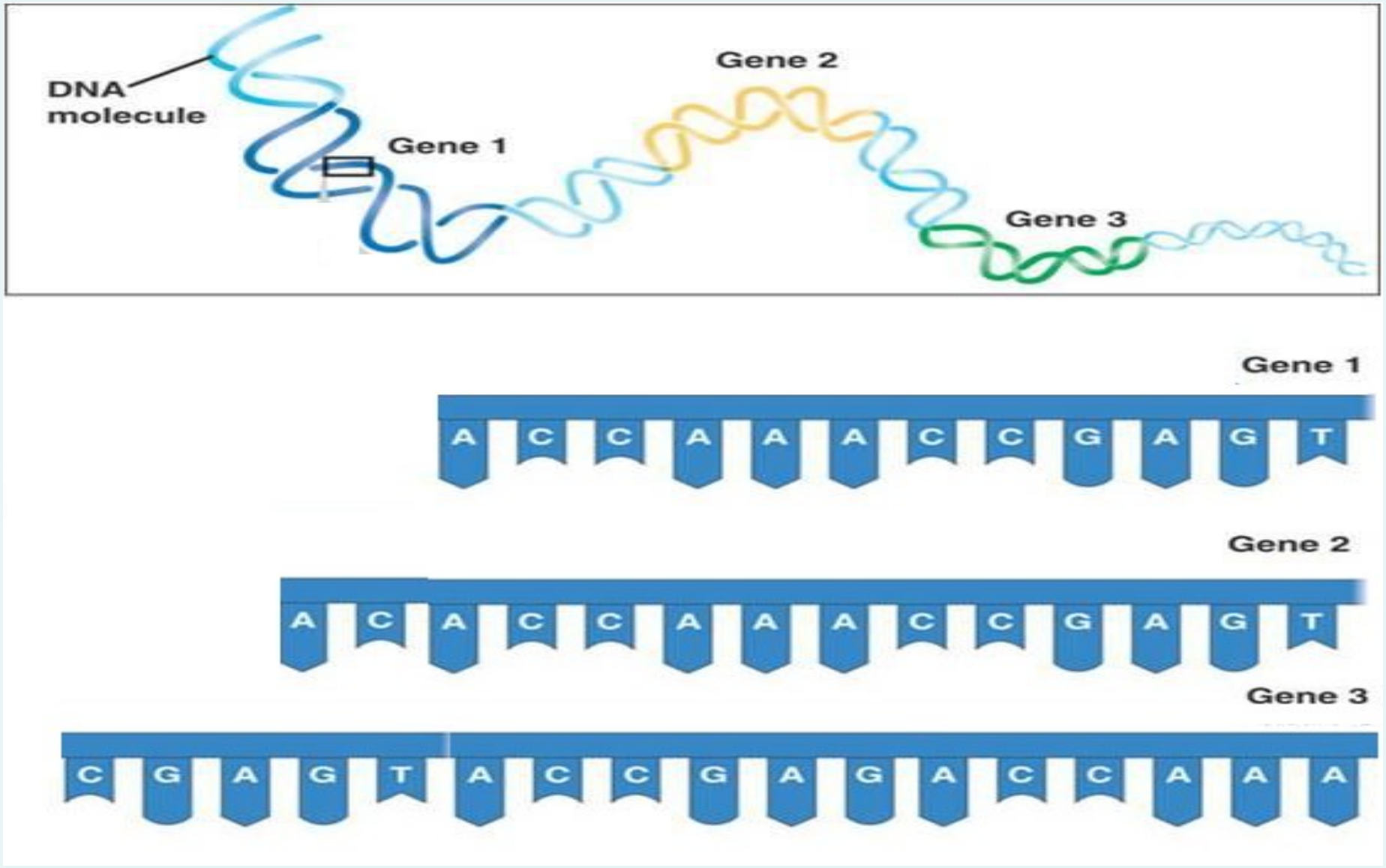
With very few exceptions, the sperm does not contain mitochondria. Nearly all mitochondria, and hence the mitochondrial genome, present in the zygote and in all body cells are descendent from the mitochondria present in the ovum at fertilization.

Structure Of Human Genes

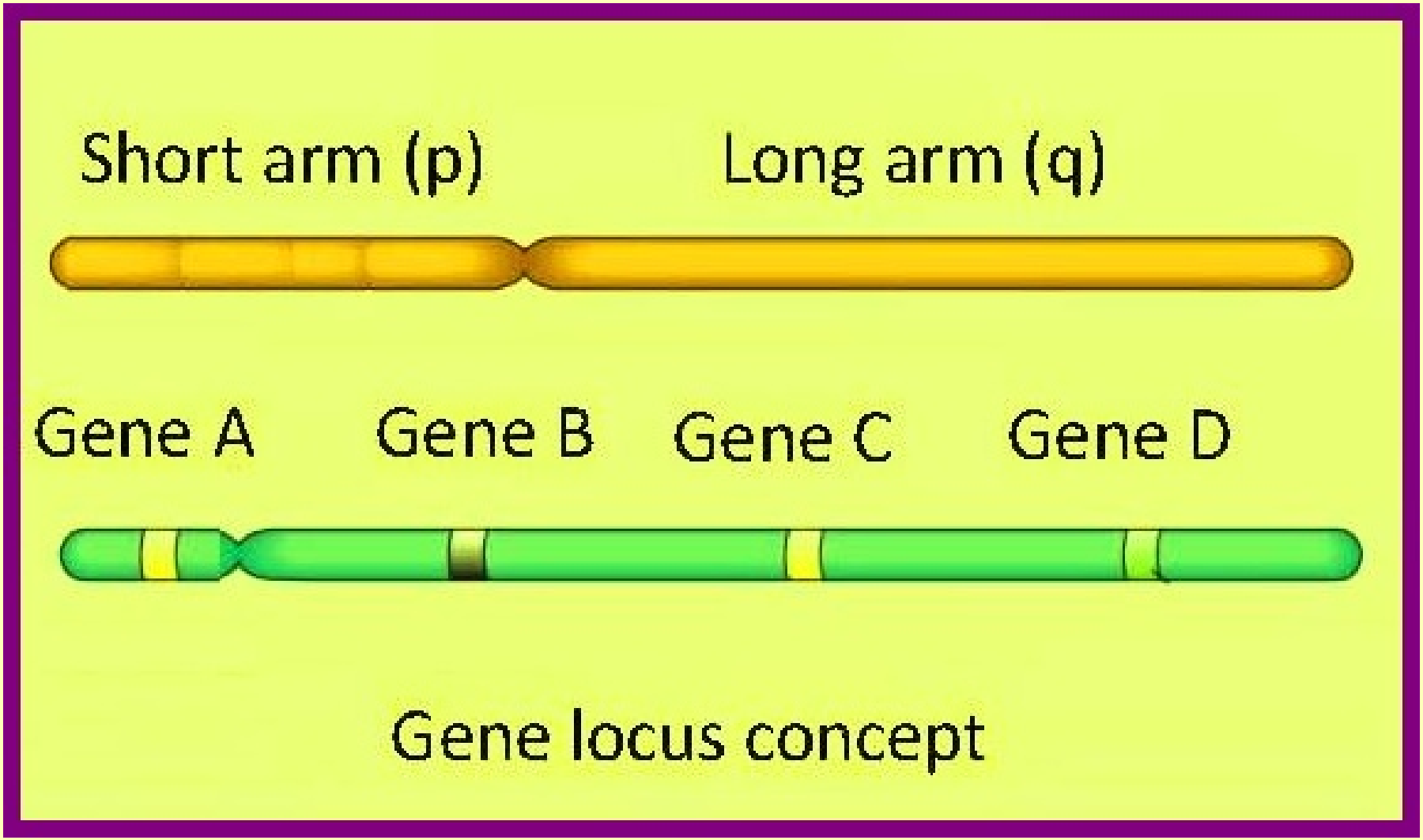
The gene, which is the functional unit of the genome, is a specified linear sequence of nucleotides along one strand of DNA (the coding or active strand). The specific site of the gene on the DNA constituting a particular chromosome is called the gene locus and is characteristic of each gene. So, a gene might occupy a specific locus on the short arm or the long arm of the chromosome.

The gene occupies a specific site on one strand of DNA. If damage to the gene occurs, the other complementary strand is used as a template to repair the gene and replace defective parts of it by a specific DNA repair system.

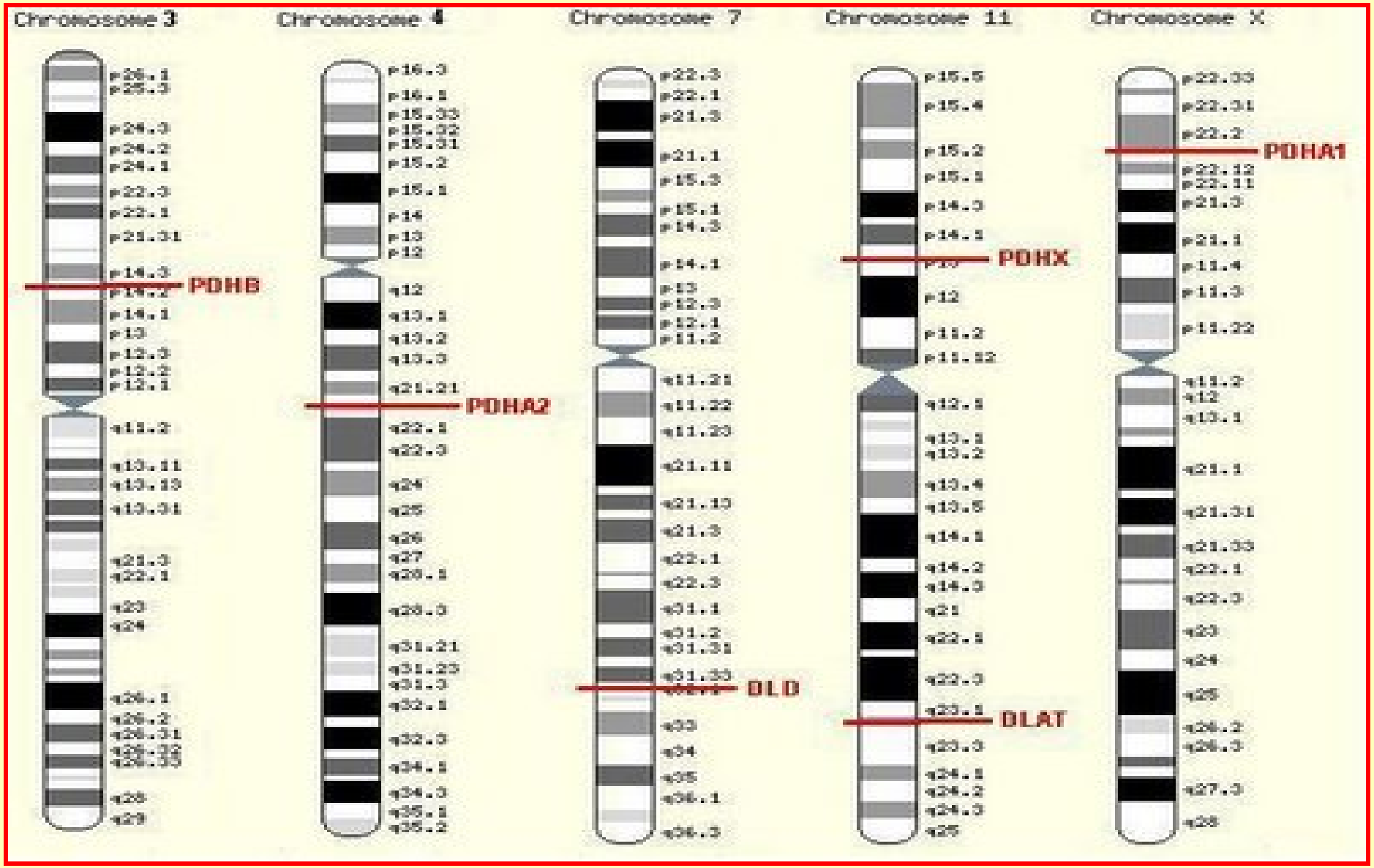
Structure of Genes and Linear arrangement of genes along DNA



Linear Arrangement Of Genes Along Chromosomes



The Concept Of Gene Locus



The estimated 38000 genes that comprise the nuclear genome constitute, and are distributed on, the 46 chromosomes in the nucleus. The longer and larger chromosomes have far more numbers of genes than the smaller and shorter chromosomes.

Genes are arranged in a linear sequence on chromosomes. Because genes constitute only a very small portion of the whole genome, they are separated by multiple long inter-genic parts of base sequences of the DNA that comprise most of the non-genic components of the genome.

All genes have the same basic structure, being composed of a long piece of DNA consisting of the 4 nucleotides (A,G,C,T), but in varying numbers and peculiar arrangement characteristic of each gene.

Some genes are formed only of few hundred nucleotides, e.g. globin genes, while others consist of many hundred thousands up to 2.4 million nucleotides which constitute the Dystrophin gene.

The specific arrangement of the nucleotides of the gene imparts to each gene its functional specificity. Functionally, genes differ from each other by the structure and nature of the protein(s) synthesized under their regulation, which is determined by the specific arrangement of the nucleotides of the gene.

The Genetic Code

1. The gene is composed of nucleotides.
2. The protein is composed of amino acids.
3. The genetic code is the information embodied within the gene that allows it to define the synthesis of a particular protein based on the number and sequence of its bases.
4. The genetic code is designed so that each three bases in sequence (triplet or codon) define a specific amino acid in the synthesized protein.
5. As the nucleotide is the structural unit of the gene, the codon is the functional unit of the gene. There are 64 codons, 61 active codon specifying amino acids and three (3) stop or termination codons that do not specify any amino acids.

The Genetic Code

TTT	Phe	TCT	Ser	TAT	Tyr	TGT	Cys
TTC	Phe	TCC	Ser	TAC	Tyr	TGC	Cys
TTA	Leu	TCA	Ser	TAA	STOP	TGA	STOP
TTG	Leu	TCG	Ser	TAG	STOP	TGG	Trp
CTT	Leu	CCT	Pro	CAT	His	CGT	Arg
CTC	Leu	CCC	Pro	CAC	His	CGC	Arg
CTA	Leu	CCA	Pro	CAA	Gln	CGA	Arg
CTG	Leu	CCG	Pro	CAG	Gln	CGG	Arg
ATT	Ile	ACT	Thr	AAT	Asn	AGT	Ser
ATC	Ile	ACC	Thr	AAC	Asn	AGC	Ser
ATA	Ile	ACA	Thr	AAA	Lys	AGA	Arg
ATG	Met*	ACG	Thr	AAG	Lys	AGG	Arg
GTT	Val	GCT	Ala	GAT	Asp	GGT	Gly
GTC	Val	GCC	Ala	GAC	Asp	GGC	Gly
GTA	Val	GCA	Ala	GAA	Glu	GGA	Gly
GTG	Val	GCG	Ala	GAG	Glu	GGG	Gly

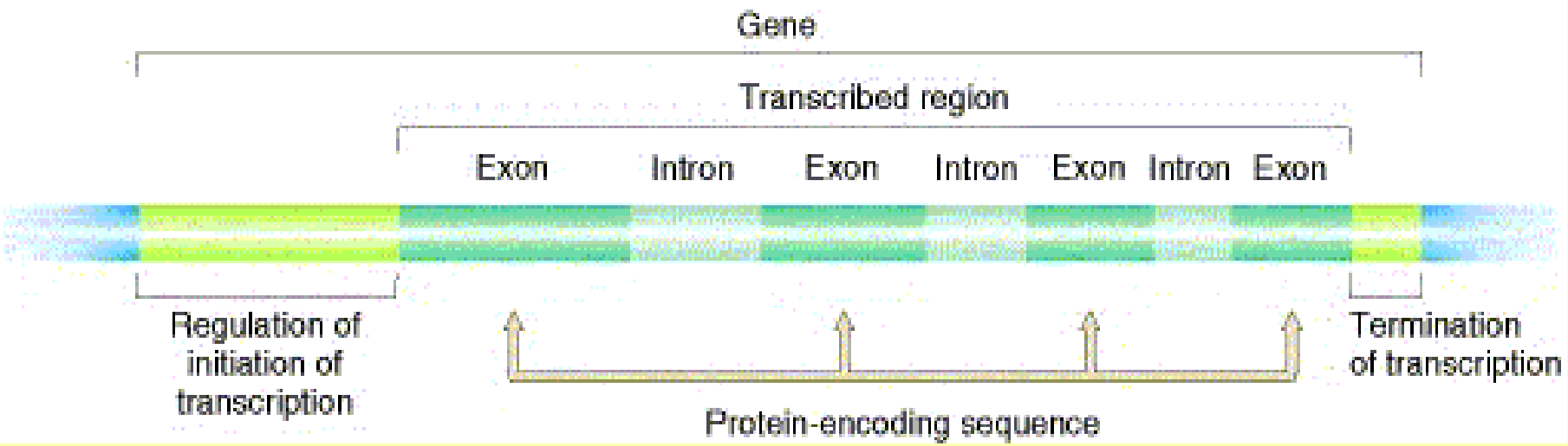
Stages Of Gene Function

1. Gene switching (stimulation/activation).
2. Transcription (synthesis of mRNA).
3. Post-transcription modifications of m-RNA

   (removal of introns and splicing of exons, addition of poly adenylate tail and many other changes)
4. Translation (synthesis of protein).
5. Post-translation modifications of Proteins

   (folding, addition of other components, etc).
6. Post-translation Trafficking of Proteins.

Functionally, the gene consists of three main parts: the promoter area responsible for switching on the gene to start function or switching it off to stop function, the exons which are the parts of the gene responsible for defining the amino acids of the protein synthesized by the gene, and the introns which are the parts of the gene which, with some exceptions, do not participate in protein synthesis.

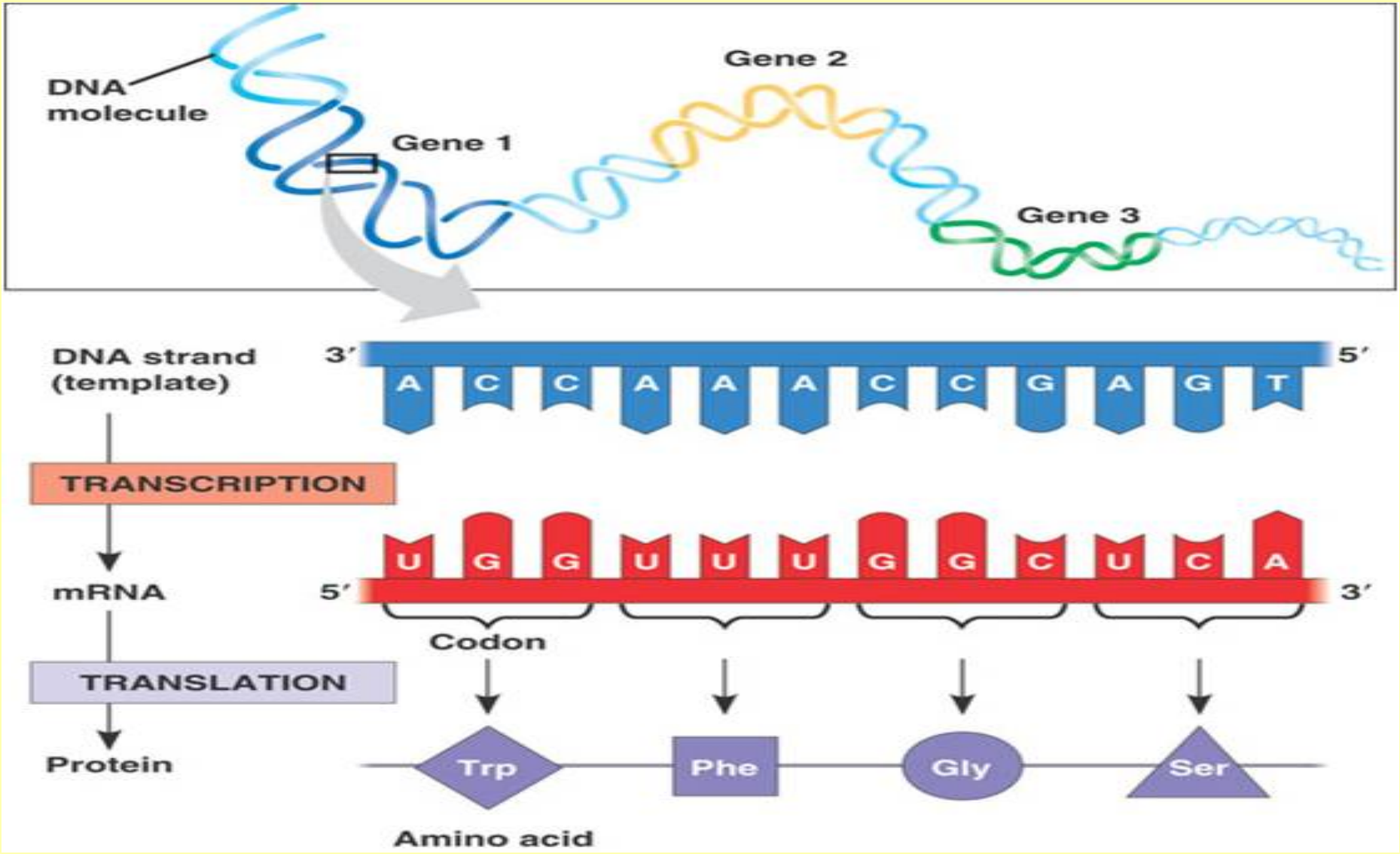


Introns are alternatively distributed along the gene with the exons and are removed from the mRNA in a process involving excision or removal of introns and splicing or joining of the exons. This process is a pre-requisite for synthesis of proper active proteins, otherwise, larger, unstable, easily degradable, physiologically non-functioning proteins, might be synthesized.

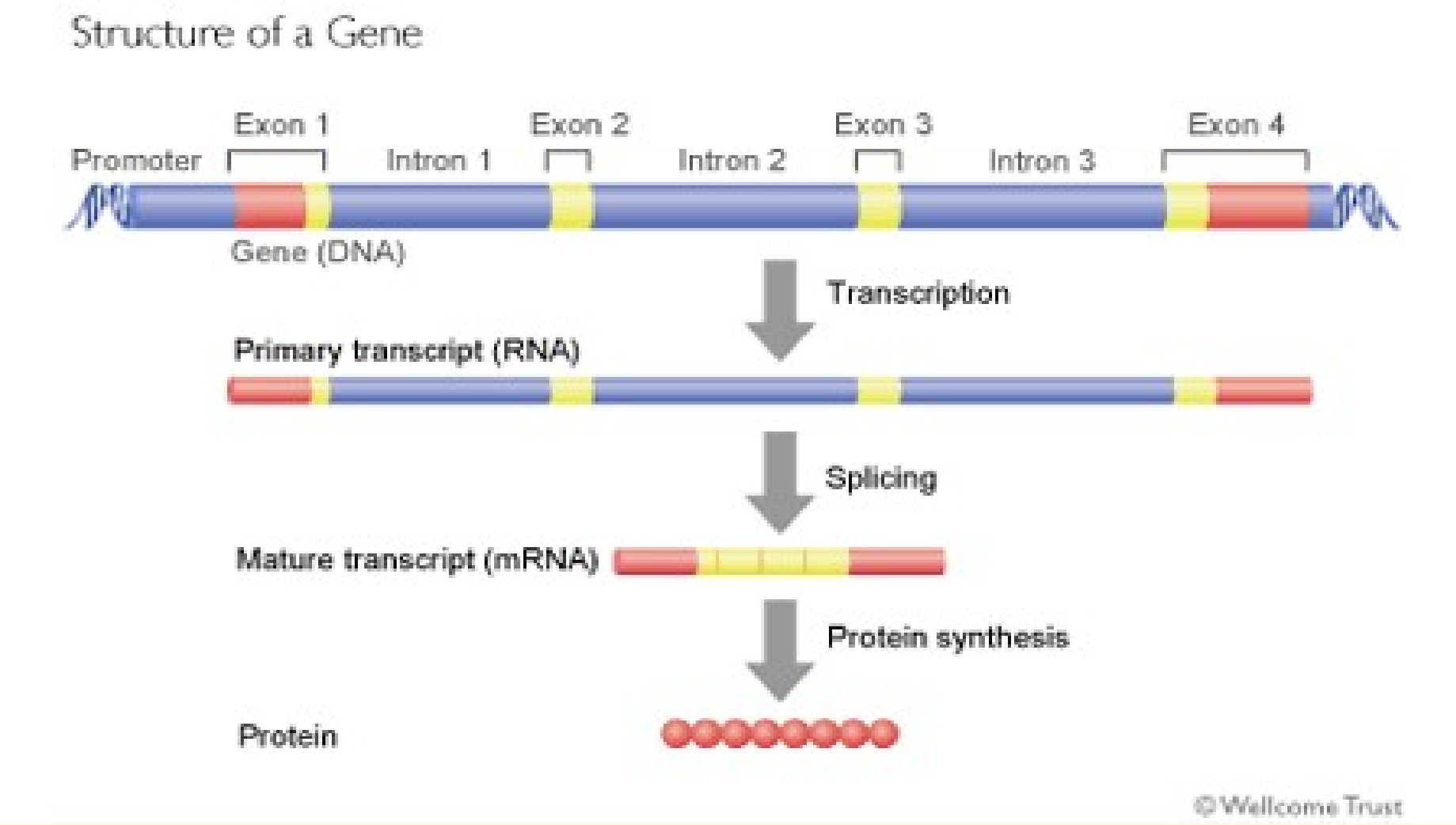
However, in some genes introns are kept in the mRNA and are translated into the protein, and via alternative removal of one or more of these introns, the gene can code for the synthesis of more than one protein.

This feature of alternative intron excision explains the huge number of proteins (nearly 400000 – 4000000) that constitute the human proteome produced under control of the far less number of genes (nearly 25000 – 38000) that constitute the human genome.

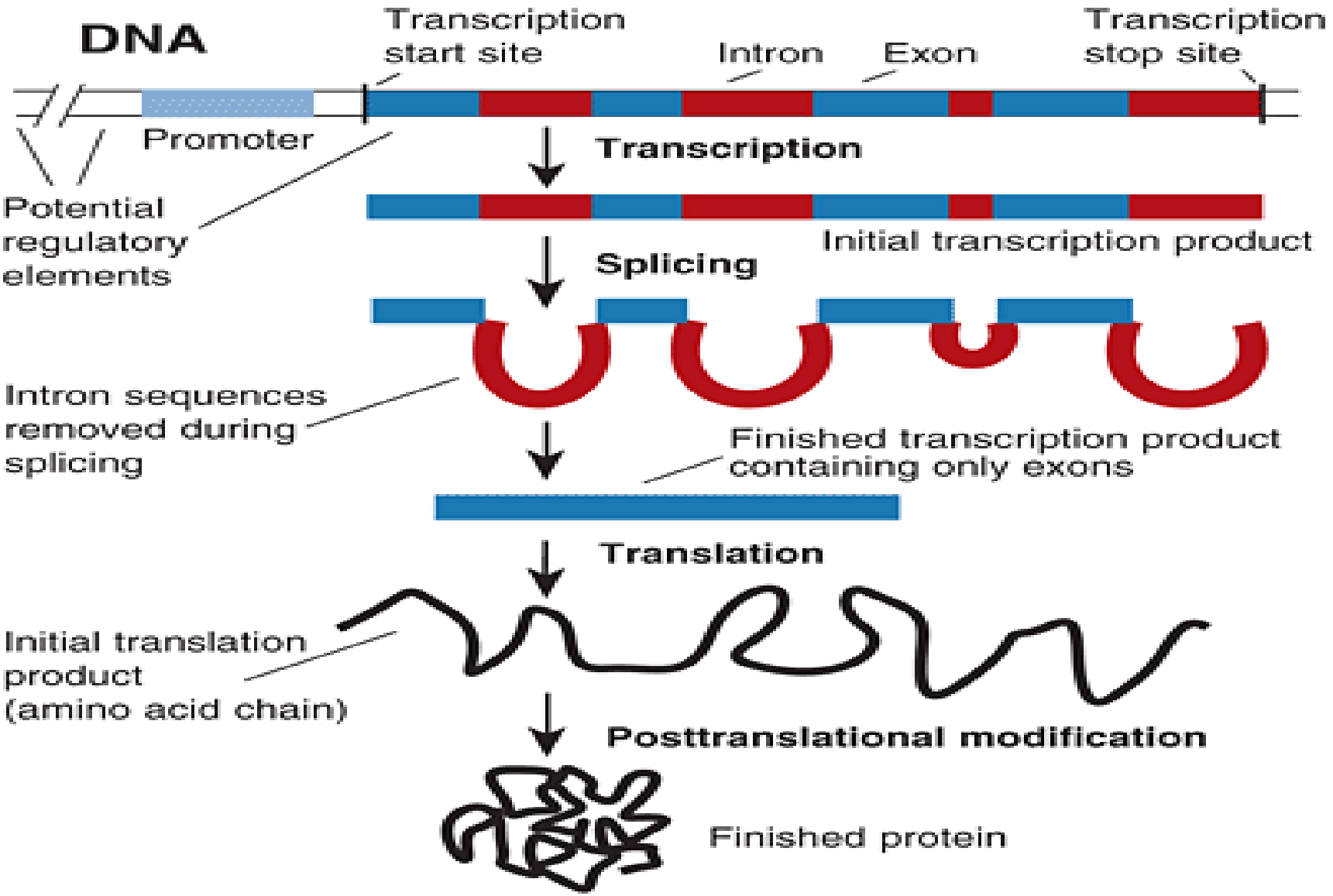
Stages Of Gene Function



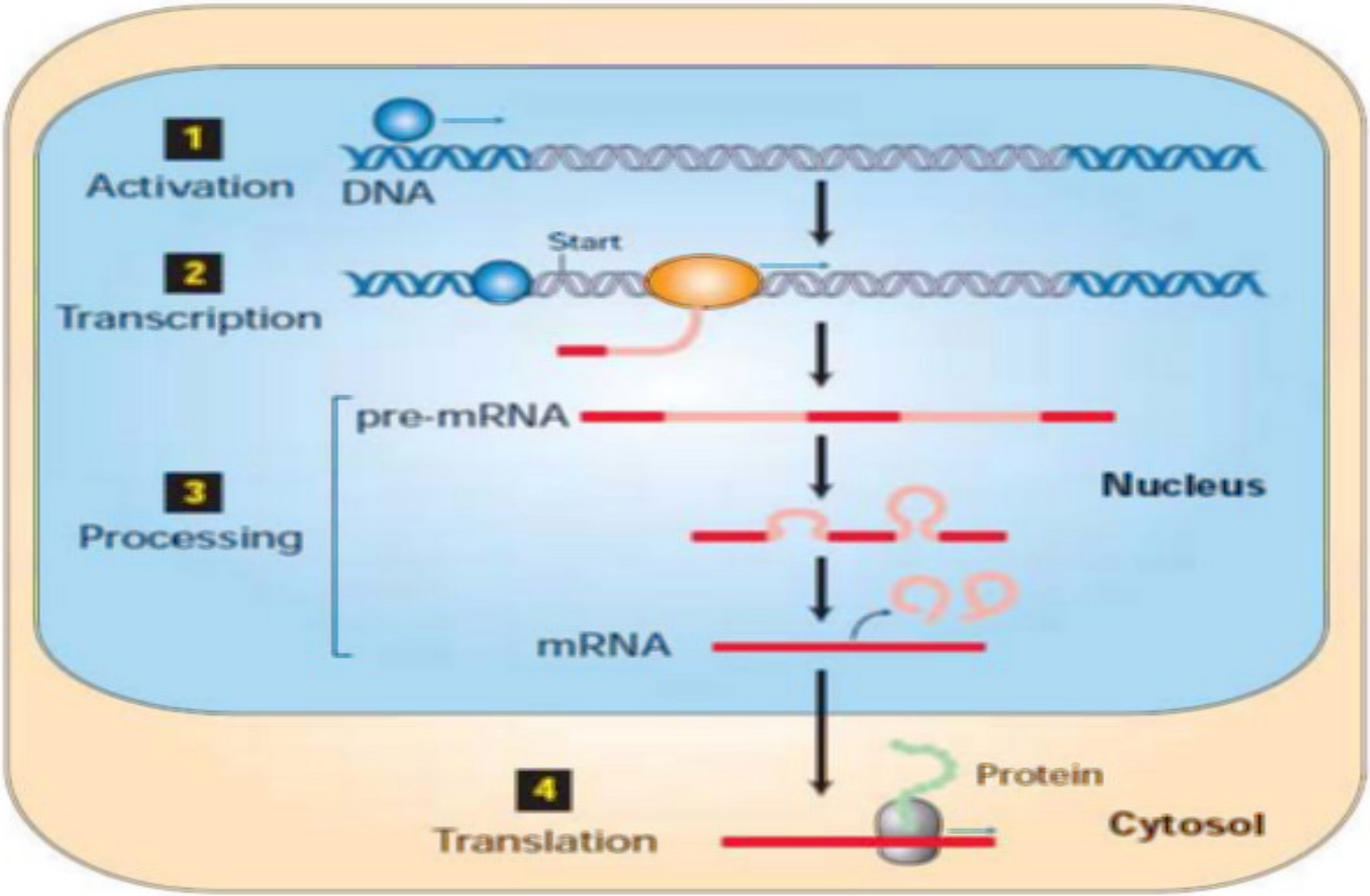
Excision of Introns and Splicing of Exons



Stages Of Gene Function



Excision of Introns and Splicing of Exons



Stages Of Protein synthesis

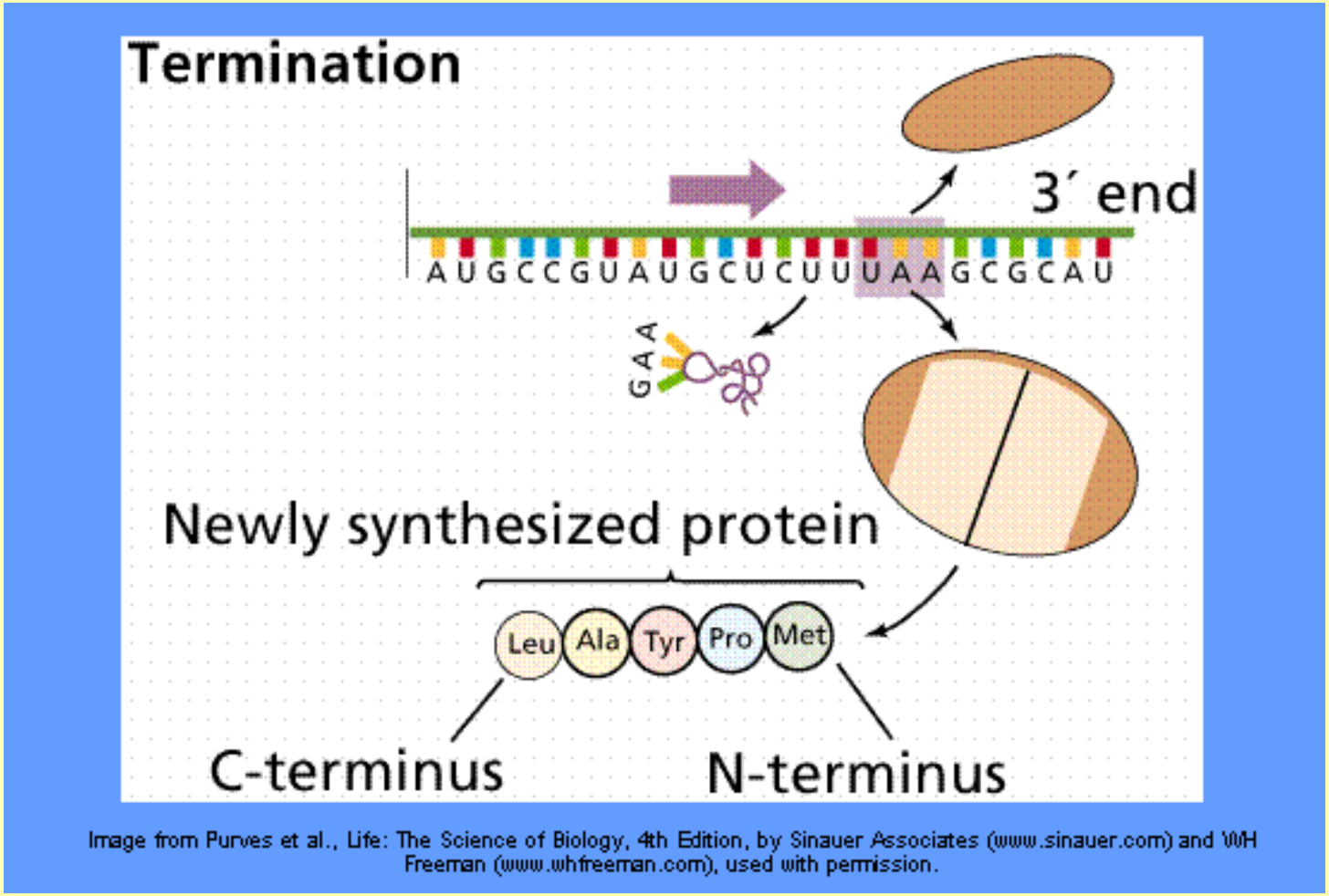
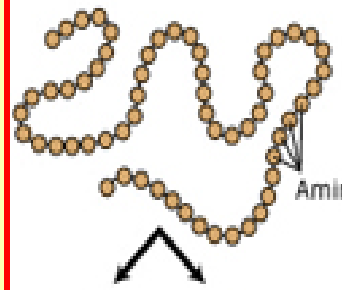


Image from Purves et al., Life: The Science of Biology, 4th Edition, by Sinauer Associates (www.sinauer.com) and WH Freeman (www.whfreeman.com), used with permission.

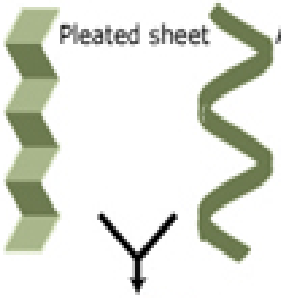
Post-translation Modifications of Proteins

The majority of newly synthesized proteins must undergo specific structural modifications, e.g. folding, to become functionally active. These modifications of protein structure are very important and critical for most proteins to confer upon them physiological potency.

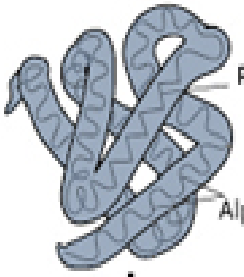
Failure of completing these structural modifications leads to production of defective proteins and underlies the development of a large number of serious genetic diseases like alph-1 antitrypsin deficiency and many immunodeficiency disorders.



Primary protein structure is sequence of a chain of amino acids.



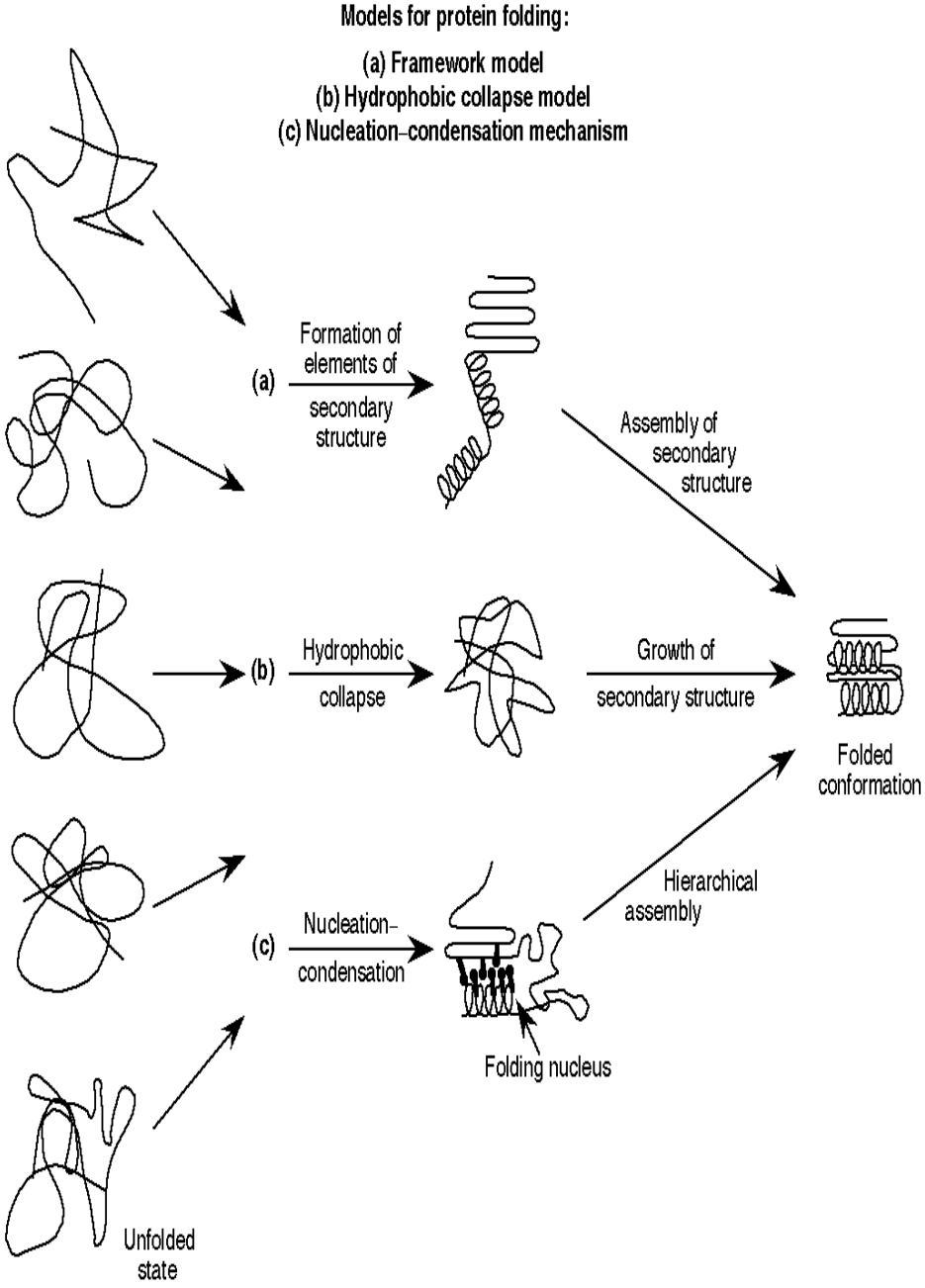
Secondary protein structure occurs when the sequence of aminoacids are linked by hydrogen bonds.



Tertiary protein structure occurs when certain attractions are present between alpha helices and pleated sheets.

Quaternary protein structure is a protein consisting of more than one amino acid chain.

Image adapted from: National Human Genome Research Institute.

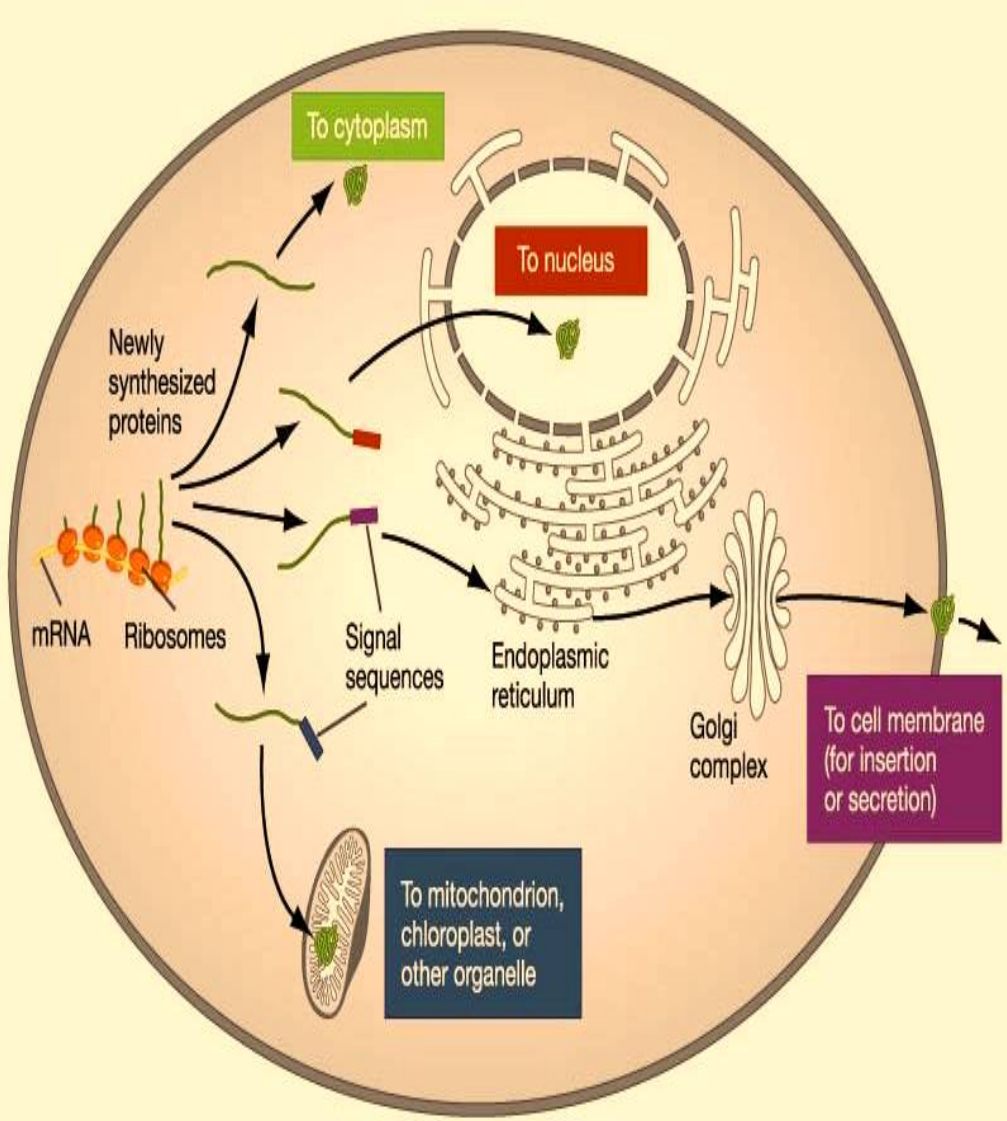


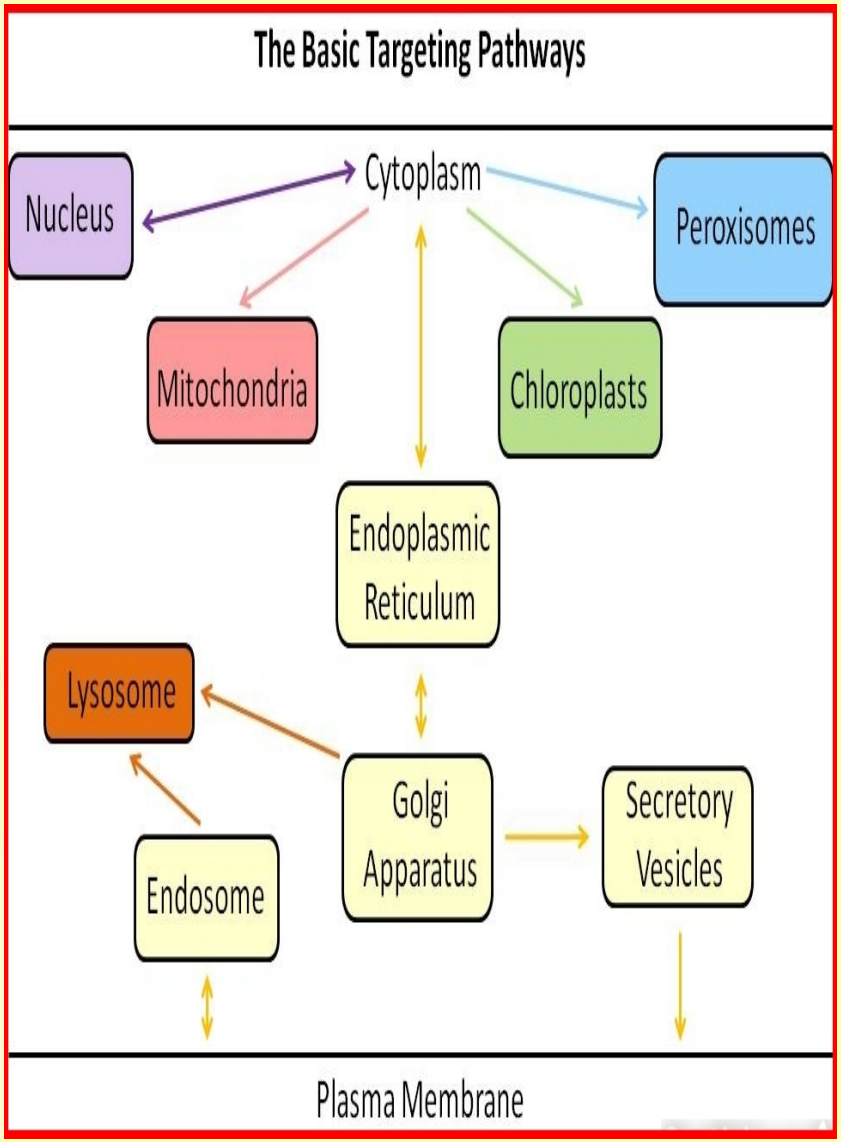
Post-translation trafficking of proteins

- **Post-translation trafficking of proteins refers to the dynamic processes that follow synthesis of new proteins, aiming at their proper localization within the cell compartments or to their extracellular locations.**

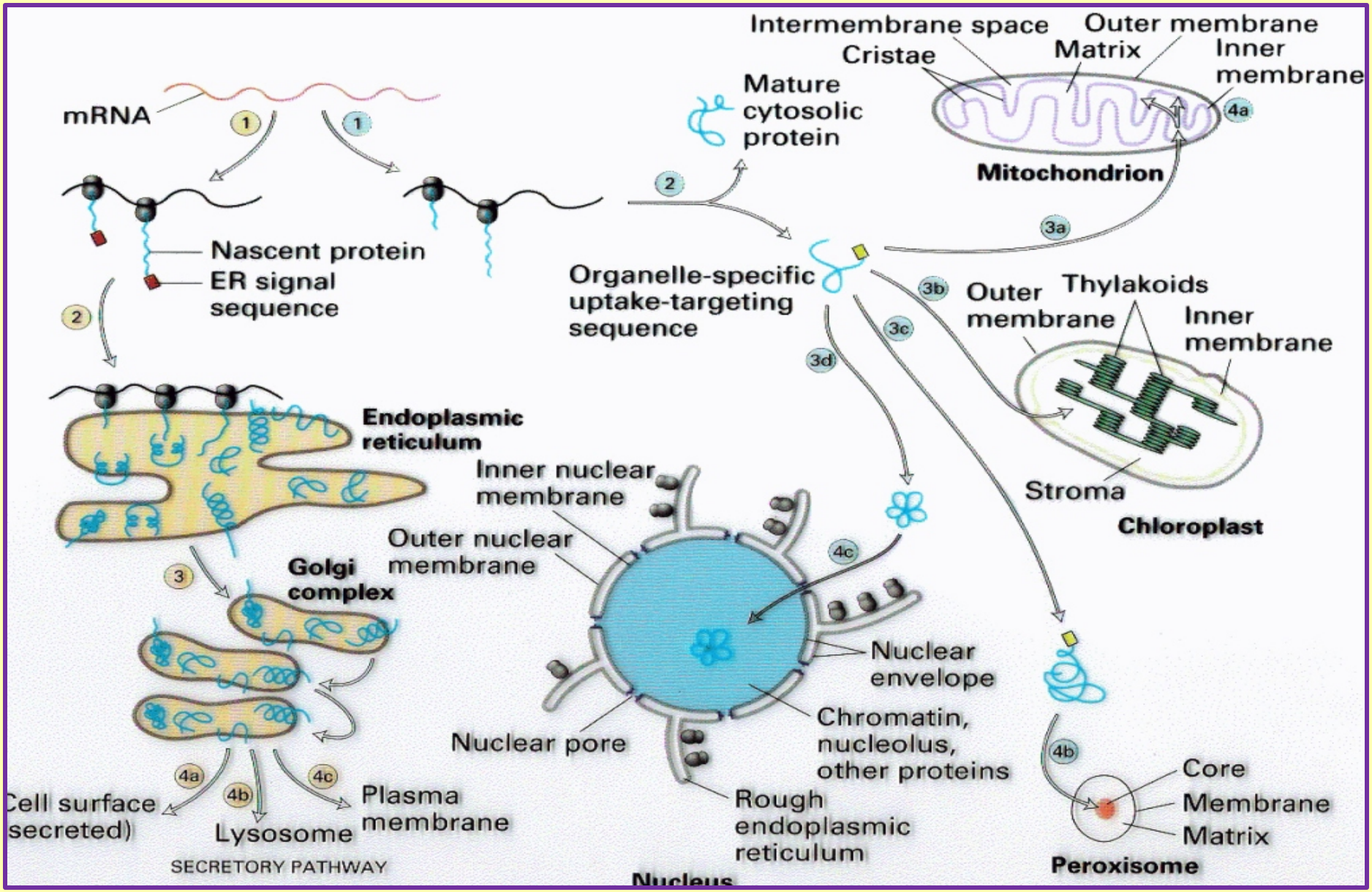
- **Defects in trafficking processes can result in disturbed localization of the protein to its target site with resultant functional deficiency of its biological and/or metabolic activities. Many genetic diseases are caused by failure of targeting properly synthesized proteins from their sites of synthesis to their sites of action.**

Post-translation trafficking of proteins





Protein Trafficking

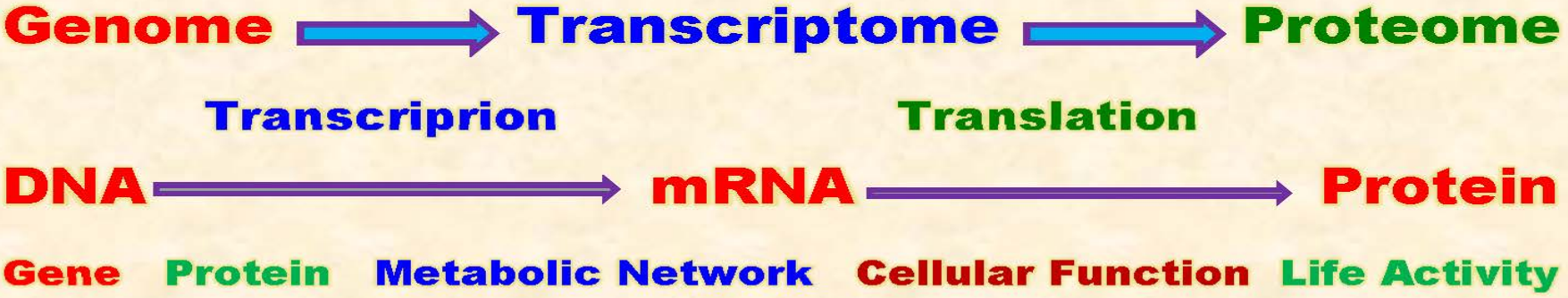


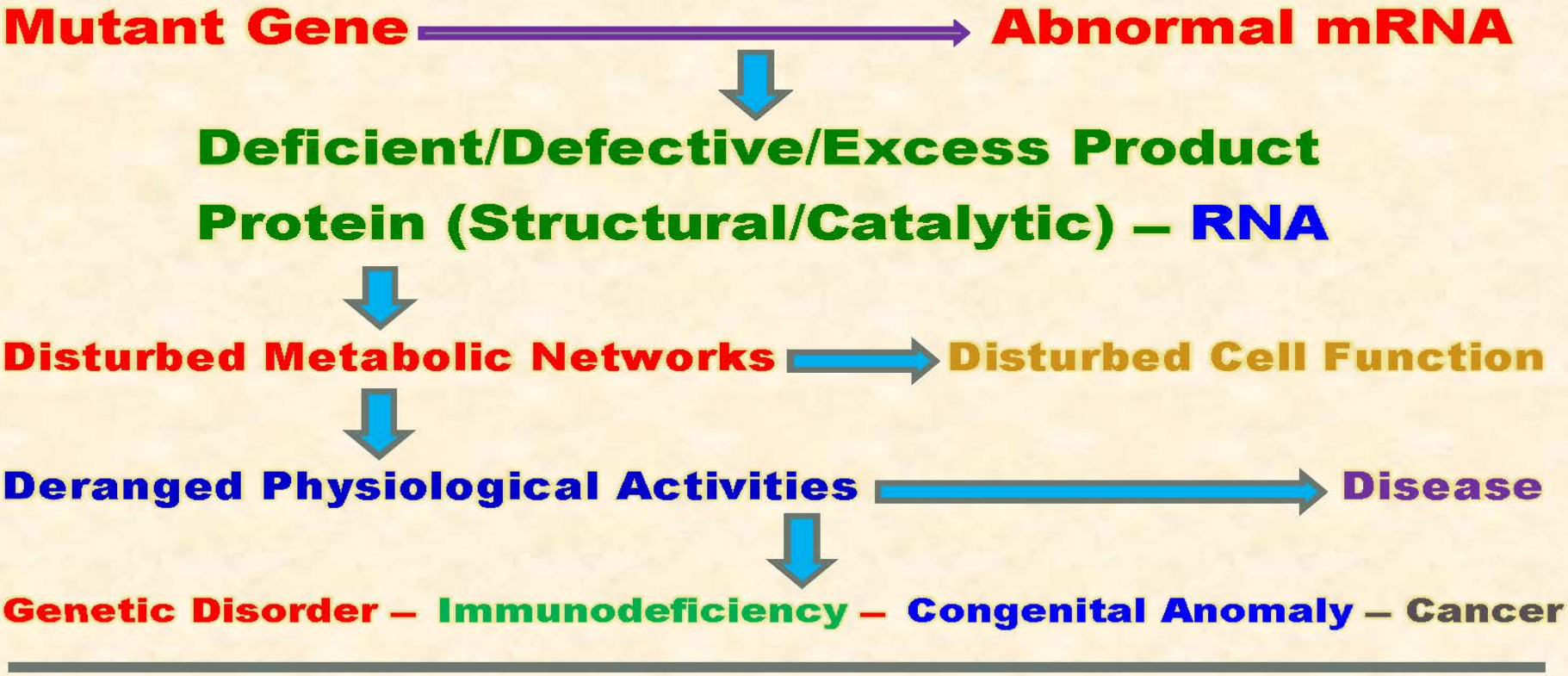
Pathogenesis Of Genetic Diseases

Genetic diseases result, primarily, from defect(s) or change(s) in structure of genes. This change in gene structure, termed mutation, in most instances results in disordered gene function leading to defective or deficient production of the gene product, or the protein.

The resulting defective or deficient protein leads to limited or widespread disorder(s) in one or more metabolic networks involving the defective protein in its pathway, thus ending ultimately in, and leading to, pathophysiological alterations and development of disease.

Dogma Of Molecular Pathology In Health And Disease





Mutation

Mutation is defined as any alteration in the structure of the genetic material at any of its organizational levels. These levels comprise: single nucleotides, DNA, RNA, genes, chromosomes, mitochondrial DNA (mtDNA), up to the whole genome. Factors that can induce mutations in the genetic material are called mutagens.

MUTAGENS

Mutagens are factors that can cause mutations. Mutagens are environmental agents potentially capable of altering or damaging the genetic material upon exposure to their effects.

The damaging effects of mutagens depend on many factors including the nature and dose of the mutagenic agent, the target of the mutational insult and the timing of exposure to the mutagenic effects in relation to specific ongoing cellular processes, like cell division, differentiation, migration and protein synthesis.

According to their nature, mutagens are classified into three main categories:

1. Chemical mutagens
2. Physical mutagens
3. Biological mutagens.

Chemical mutagens comprise countless numbers of chemical compounds like simple and complex organic compounds, insecticides, asbestos, herbicides, heavy metals, etc.

Physical mutagens include particulate radiations like alpha and beta particles, solar radiation, UV waves, thermal and mechanical agitation of nucleic acids, etc.

Biological mutagens include living microorganisms like many types of viruses (rubella, cytomegalovirus, herpes virus), and Toxoplasma.

According to their effects, mutagens are classified into four main categories:

1. **Carcinogens**
2. **Clastogens**
3. **Teratogens**
4. **Non-specific Mutagens.**

Carcinogens are mutagenic agents capable of inducing malignant transformations in affected cells.

Clastogens are mutagenic agents that cause chromosome breaks in affected cells.

Teratogens are mutagenic agents that induce development of malformations in embryos and fetuses exposed to their effects.

Non-specific mutagens are mutagens that cause non-specific deleterious effects of the genetic material.

Mutagens : types, effects and exa

Mutagens	Effects	Examples
Carcinogens	Carcinogenesis And Tumor Formation.	Chemical : Aflatoxins Biological : Retroviruses Physical : X-ray Irradiation
Clastogens	Chromosome Breaks, Deletions, Rearrangements.	Chemical : Bleomycin Biological : HIV virus Physical : X-ray Irradiation
Teratogens	Congenital Malformations.	Chemical : Valproate Biological : Toxoplasma G Physical : X-ray Irradiation
Non-specific Mutagens	Non-specific Damage To The Genetic Material.	Chemical : Innumerable Physical : X-ray Irradiation Biological : Toxoplasma, Viruses

TYPES OF MUTATION

1. Spontaneous versus Induced
2. Somatic versus Germinal
3. Nuclear versus Mitochondrial
4. Static versus Dynamic
5. Persistent versus Reversible
6. Point . Genic . Chromosomal . Genomic
7. Base . Sugar . Phosphate group.
8. Pathological versus Non-Pathological

According to the extent and magnitude of the mutation-induced damage of the genetic material, mutations might be classified into four major categories :

1. Point mutations
2. Small mutations
3. Gross mutations
4. Genomic mutations.

Point mutations involve deletion, addition or change of one single base, or nucleotide, of the gene.

Small mutations involve deletion, addition or change of two or more bases up to large segments of the gene.

Gross mutations involve large changes comprising deletions, duplications, inactivation and rearrangements of one or more genes or one or more chromosomes.

Genomic mutations affect the whole nuclear genome either via inactivation (imprinting) or reduplication.

Quantitative Classification of Mutation

According to the target of mutation, four major types of mutation can be delineated:

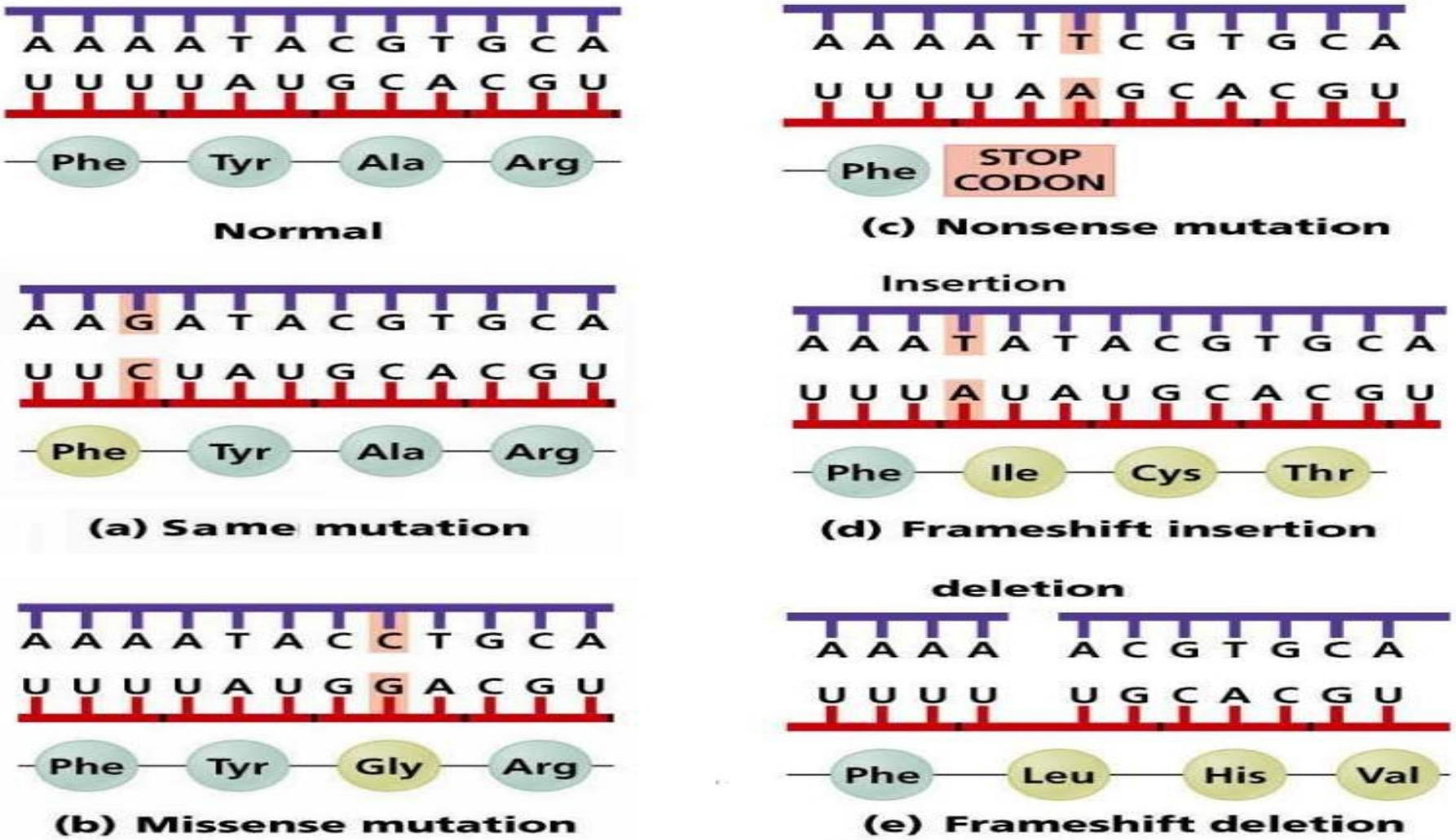
1. Point mutation caused by change of one single base. It comprises five different types: missense, same sense, non-sense, re-sense and single base frame shift mutation.

2. Small mutation involving more than one base up to parts of genes or few genes.

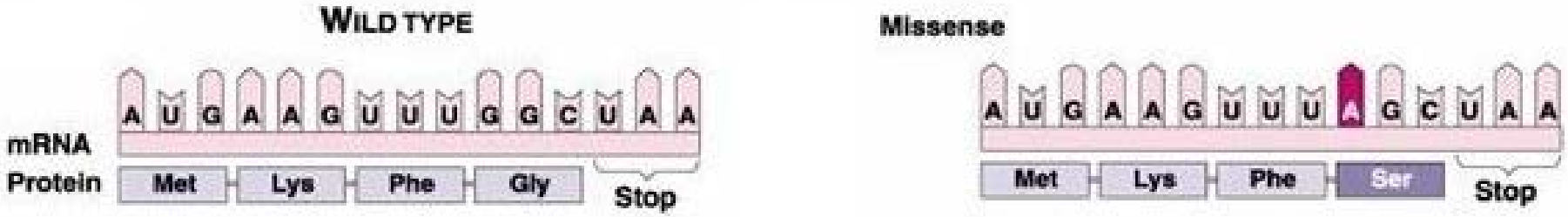
3. Gross mutation comprising chromosomal aberrations.

4. Genomic mutation involving the whole genome, either the haploid (23) germ cell genome or the diploid (46) somatic genome (triploidy, tetraploidy, genomic imprinting).

1. Types of Point Mutations



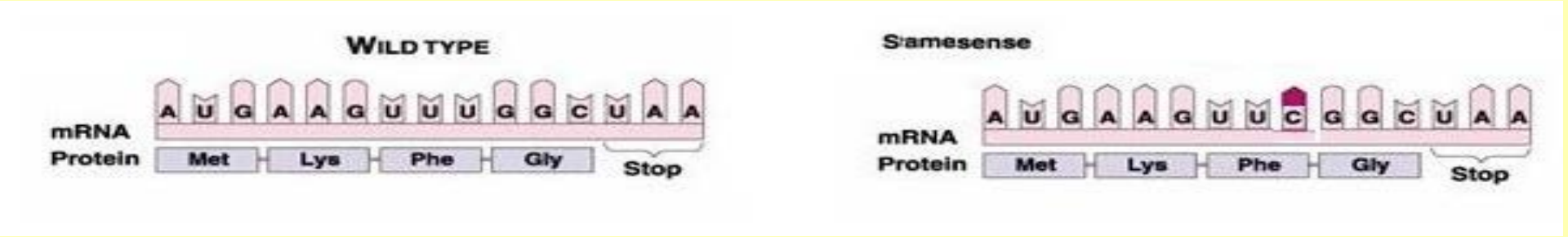
1. Mis-sense mutation



In this type of point mutation, change of one nucleotide of a codon specifying a specific amino acid by another nucleotide might change the codon to a different codon specifying a different amino acid. For example, change of (GGC) coding Glycine to (AGC) coding Serine.

If the wild type amino acid mediates a particular function in the protein that can not be performed by the new amino acid, then defect(s) in protein function(s) might result leading, in most instances, to altered pathophysiological effect(s) and disease according to the altered function of the new protein.

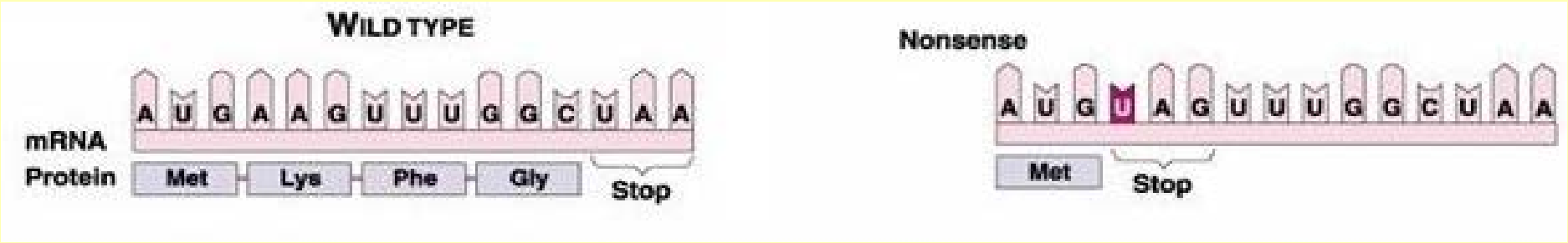
2. Same-sense mutation



In this type of point mutation, replacement of one nucleotide of a codon specifying a particular amino acid by another nucleotide, turning the codon into another codon specifying the same amino acid, due to degeneracy of the genetic code, occurs. For instance, change of (UUU) coding Phenylalanine to (UUC) which, also, codes Phenylalanine.

In this type of point mutation, no change(s) in the protein function(s) occur since the protein has the same native structure, and no pathophysiological alterations are noted and no disease(s) develops.

3. Non-sense mutation



This type of point mutation entails change of one nucleotide of a functional codon by another nucleotide turning the codon into a stop codon. For example, change of (AAG) coding Lysine to (UAG) which is a Termination or Stop codon that do not code any amino acids. These mutations cause cessation of translation, truncation or premature termination of protein synthesis and production of shorter incomplete proteins. If the missing part of the protein is functionally important, these mutations result in functional deficiency, pathophysiological alterations and development of disease state.

2. Genic/Small Mutations

1. Loss/damage of part(s) of one or more nuclear genes (one or multiple exons/introns).
2. Loss of one or few genes.
3. Loss/damage of part(s) of mitochondrial genome
4. Loss of regulatory intergenic sequences leading to various functional defects:

   . DNA replication/repair defects

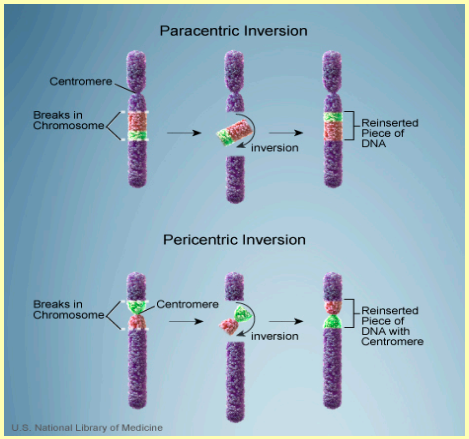
   . Splicing defects mutations

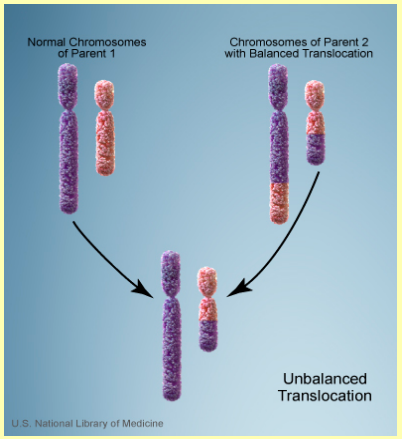
   . Telomere defects mutations

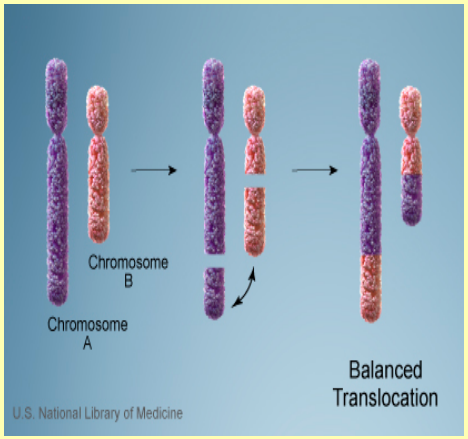
   . Transposon over activity defects.

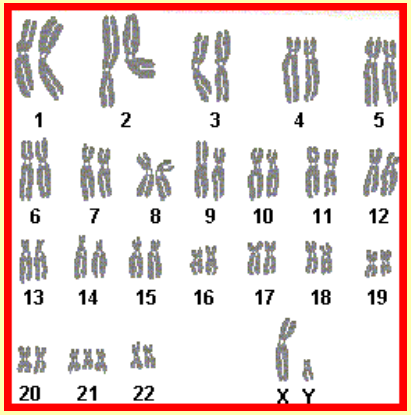
3. CHROMOSOMAL MUTATIONS

Structural Mutations	Numerical Mutations
1. Deletion	1. Trisomy (47 Chromosomes)
2. Translocation	2. Monosomy (45 Chromosomes)
3. Insertion	3. Hypodiploidy (Less than 46)
4. Ring chromosome formation	4. Hyperdiploidy (More than 46)
5. Dicentric chromosome formation	5. Triploidy (3N : 69 Chromosomes)
6. Chromosome gaps and breaks	6. Tetraploidy (4N : 92 Chromosomes)


Paracentric Inversion
Centromere
Breaks in Chromosome
inversion
Reinserted Piece of DNA
Pericentric Inversion
Breaks in Chromosome
Centromere
inversion
Reinserted Piece of DNA with Centromere
U.S. National Library of Medicine


Normal Chromosomes of Parent 1
Chromosomes of Parent 2 with Balanced Translocation
Unbalanced Translocation
U.S. National Library of Medicine


Chromosome B
Chromosome A
Balanced Translocation
U.S. National Library of Medicine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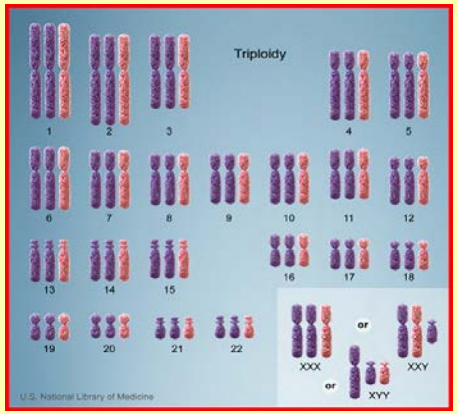
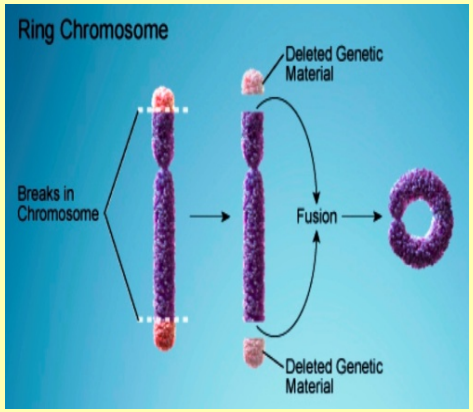
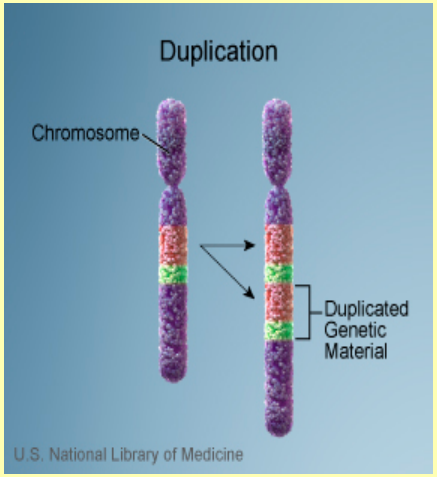
X Y


Triploidy
U.S. National Library of Medicine


Ring Chromosome
Deleted Genetic Material
Breaks in Chromosome
Fusion
Deleted Genetic Material


Duplication
Chromosome
Duplicated Genetic Material
U.S. National Library of Medicine

Chromosomal Abnormalities

A. Autosomal abnormalities

1. Autosomal Numerical Abnormalities
2. Autosomal Structural Anomalies

B. Sex chromosomal abnormalities

1. Sex Chromosomes Numerical abnormalities
2. Sex chromosomes Structural abnormalities

C. Genome abnormalities

1. Triploidy (69 chromosomes)
2. Tetraploidy (92 chromosomes)

A. Autosomal abnormalities

Autosomal Numerical Abnormalities

a. Trisomy 47 chromosomes

b. Monosomy less than 45 chromosomes: lethal, incompatible with life.

c. Hypodiploidy less than 45 chromosomes

d. Hyperdiploidy more than 47 chromosomes

Autosomal Structural Anomalies

Deletions, translocations, isochromosomes, inversions, instability, insertions, gaps, transposition, etc.

B. Sex chromosomal abnormalities

Sex chromosomes Numerical Abnormalities

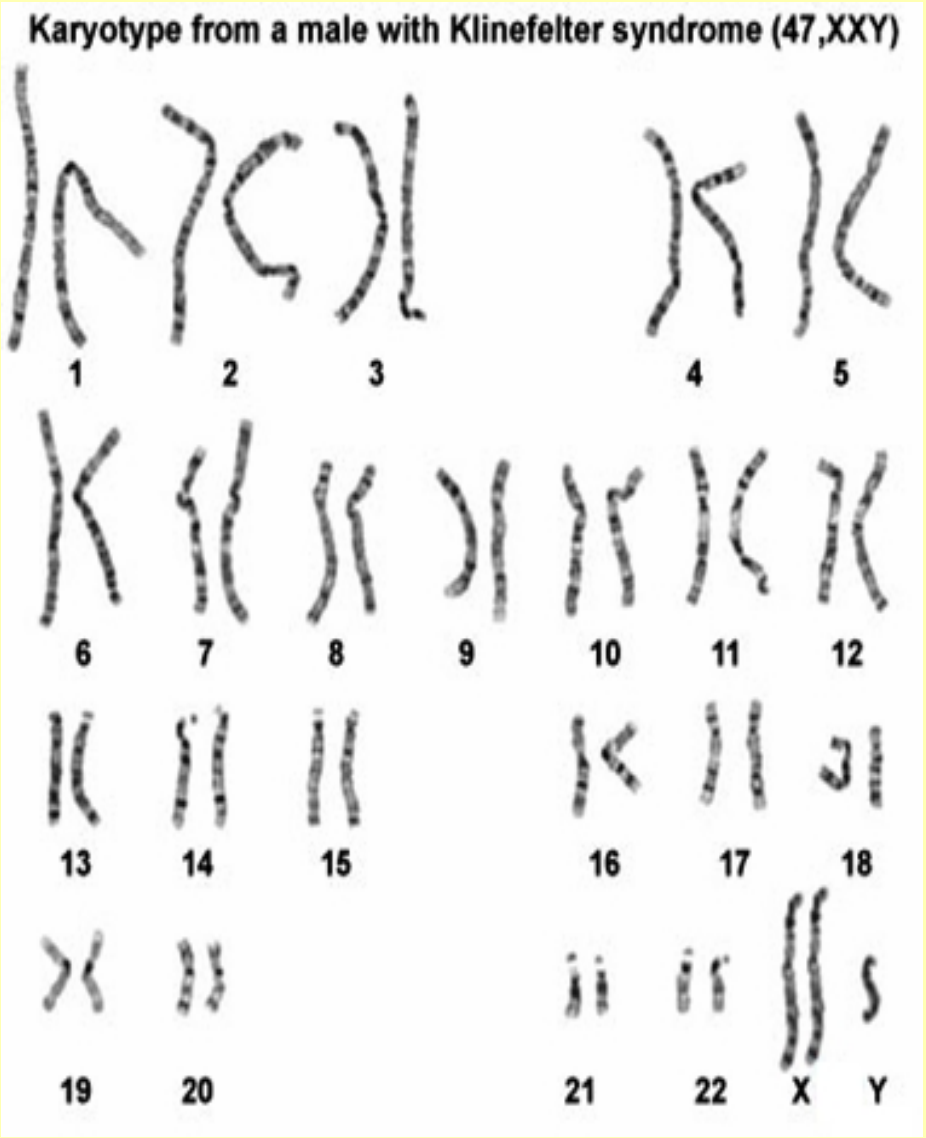
1. X-chromosome monosomy: Turner syndrome: 45,X (complete/partial monosomy).
2. 47,XXY: Klinefelter syndrome.
3. Multiple X syndromes: 48,XXX/49,XXXX syndrome
4. 47,XYY syndrome.

Sex chromosomes Structural Abnormalities

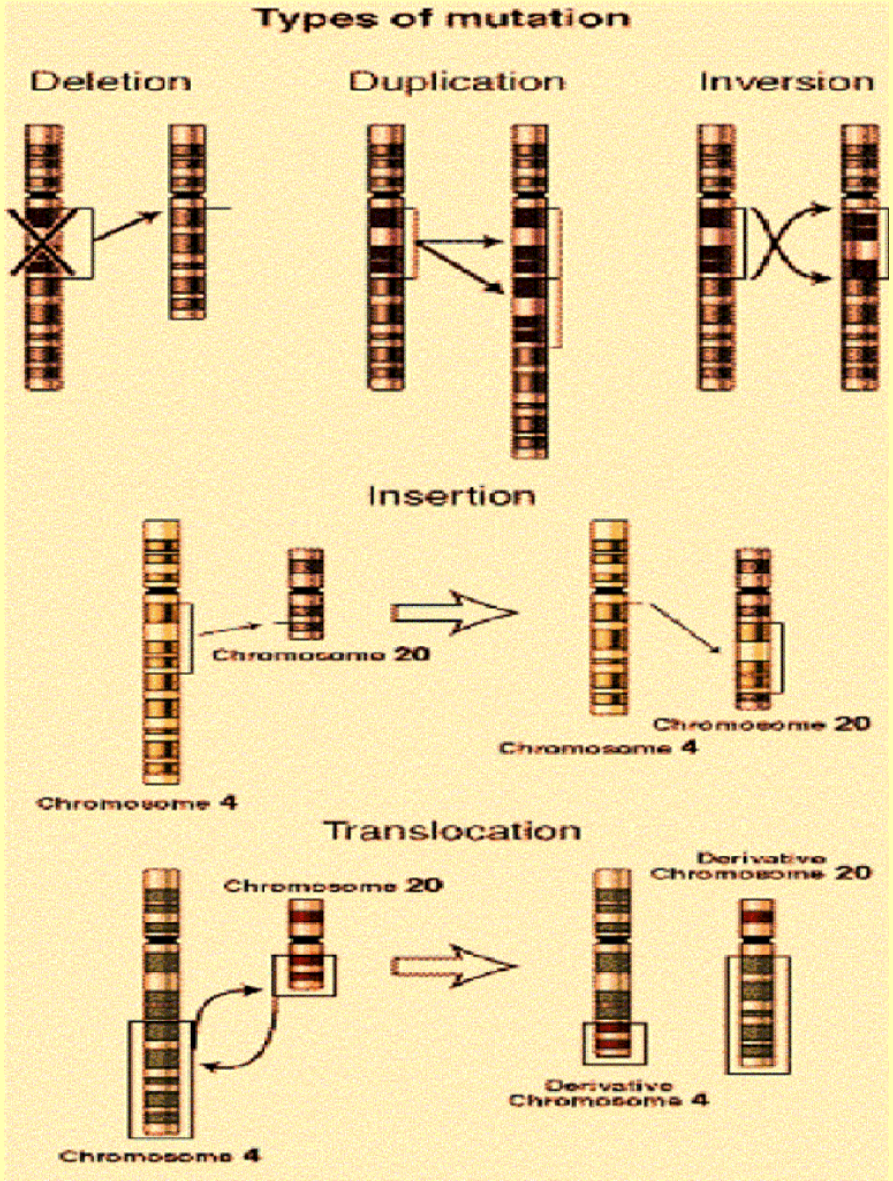
X-chromosome ring formation, partial deletion, isochromosome formaton, etc.

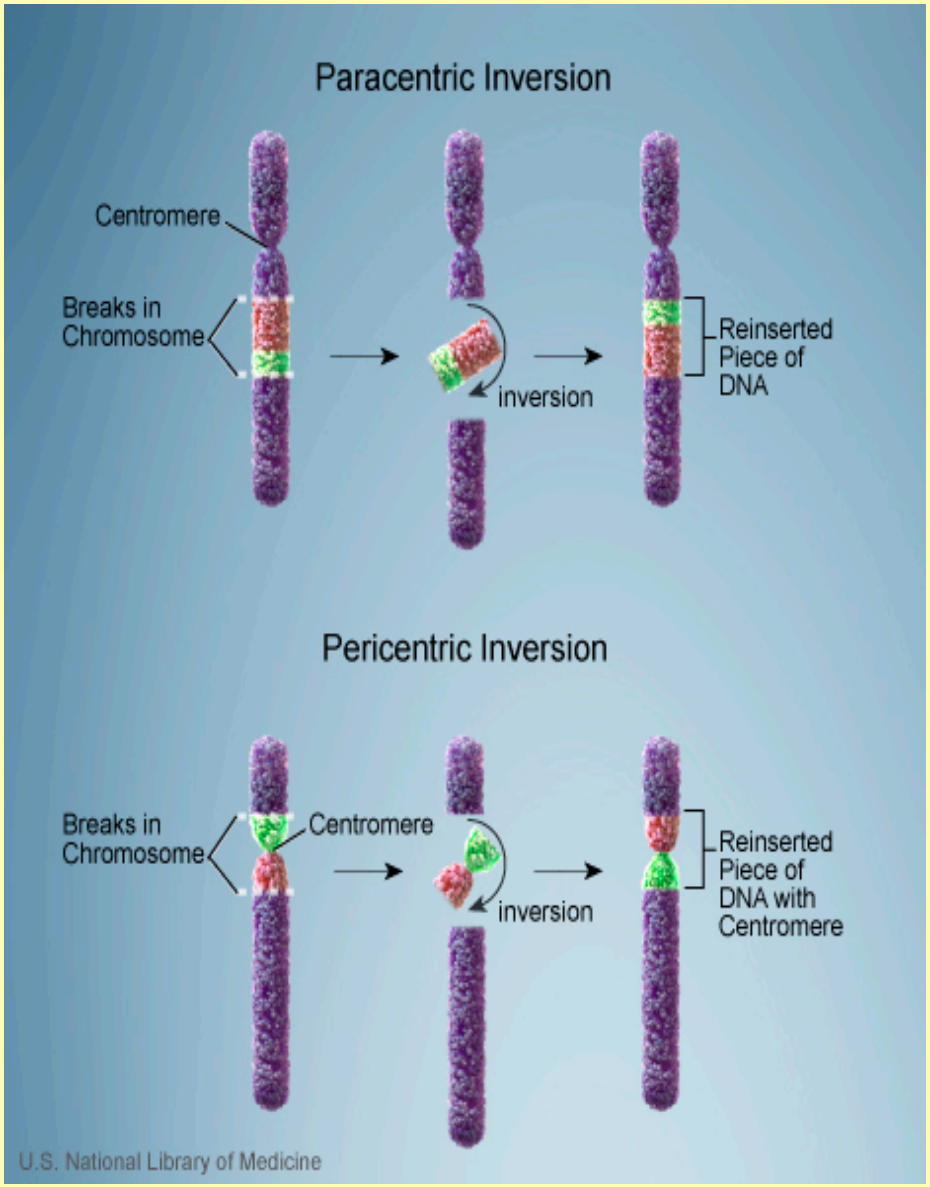
Y-chromosome deletions, microdeletions, eyc.

Numerical Chromosomal Abnormalities



Structural Chromosomal Abnormalities





Pathogenesis Of Genetic Diseases

Genetic diseases are caused by mutations, or structural changes of the genetic material at any of its organizational levels. Mutations cause disturbances and alterations of the structure and / or function of the genetic material, leading ultimately to one or more of the following consequences :

1. Deletion, or loss, of part of a gene, one or many genes, part of a chromosome, one or more chromosomes, one or more of mitochondrial genes, or even a whole genome.
2. Duplication / Rearrangement of the genetic material.
3. Deficient / Defective transcription of mRNA.
4. Deficient / Defective post-transcriptional modifications of mRNA.
5. Deficient / Defective translation of mRNA leading to deficient / defective production of gene products.
6. Deficient / Defective post-translational modifications of proteins.

7. Deficient / Defective production of regulatory factors. These include microRNA, transcription nucleoproteins, etc.

Irrespective of the site, type, nature or magnitude of the mutational event(s) that drastically affect the genetic material, the resultant alterations in gene function(s) trigger many disturbances in one or more of the cellular metabolic regulatory networks mediated by the deficient / defective gene products, thus leading to a wide and varied spectrum of pathophysiological changes in cellular functions leading, ultimately, to development of genetic diseases.

The specific pathognomonic phenotype that characterizes each genetic disease is primarily determined by the spectrum of pathophysiological changes in affected subjects. These, in turn, are determined by the spectrum of the mutation-induced damage to the genetic material in affected patients.

Pathogenesis Of Genetic Diseases
Structural Gene Mutations

Mutation

↓

Change Of Gene Structure

↓

Promotor Mutations → Suppression & Loss Of Gene Function
Disturbance In Transcription

↓

Defective mRNA Processing / Repair

↓

Disturbed / Defective mRNA Translation

↓

Deficient Synthesis Of Protein
Synthesis Of Defective Protein
Defective Post-Translation Modifications
Defective Protein Repair
Disturbances In Metabolic Networks

↓

Protein Deficiency Disorders . Albinism
Inborn Errors Of Metabolism
Oxidative-Phosphorylation Defects

www.archive.org/details/MedicalGenetics